Vol. 35 No. 182 August, 1960

ARCHIVES OF DISEASE IN CHILDHOOD

EDITORS
I. A. B. CATHIE and RICHARD H. DOBBS

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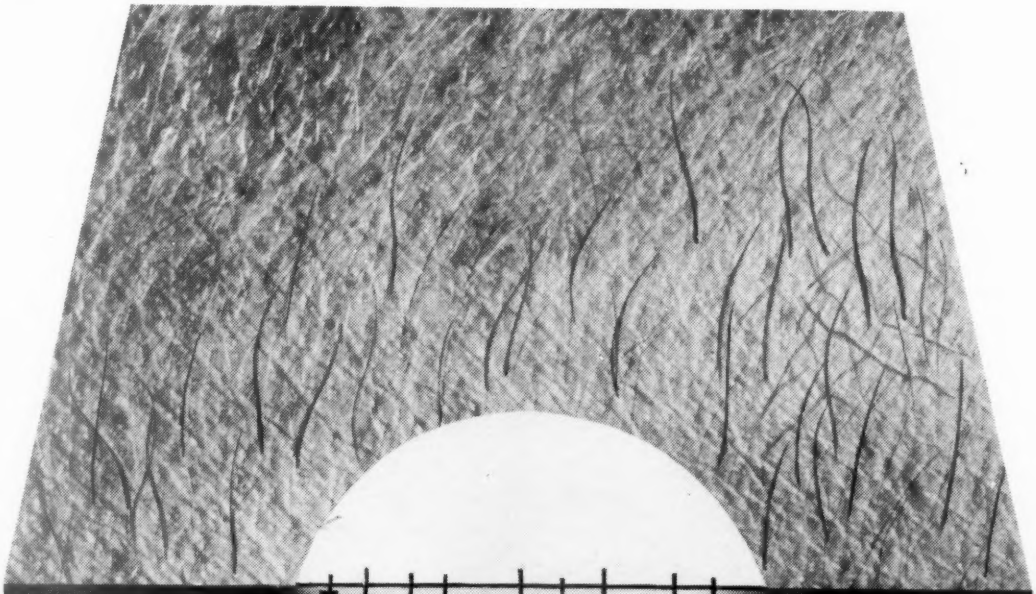

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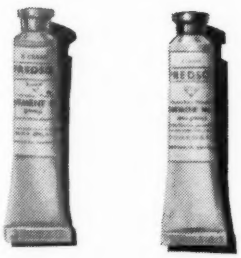

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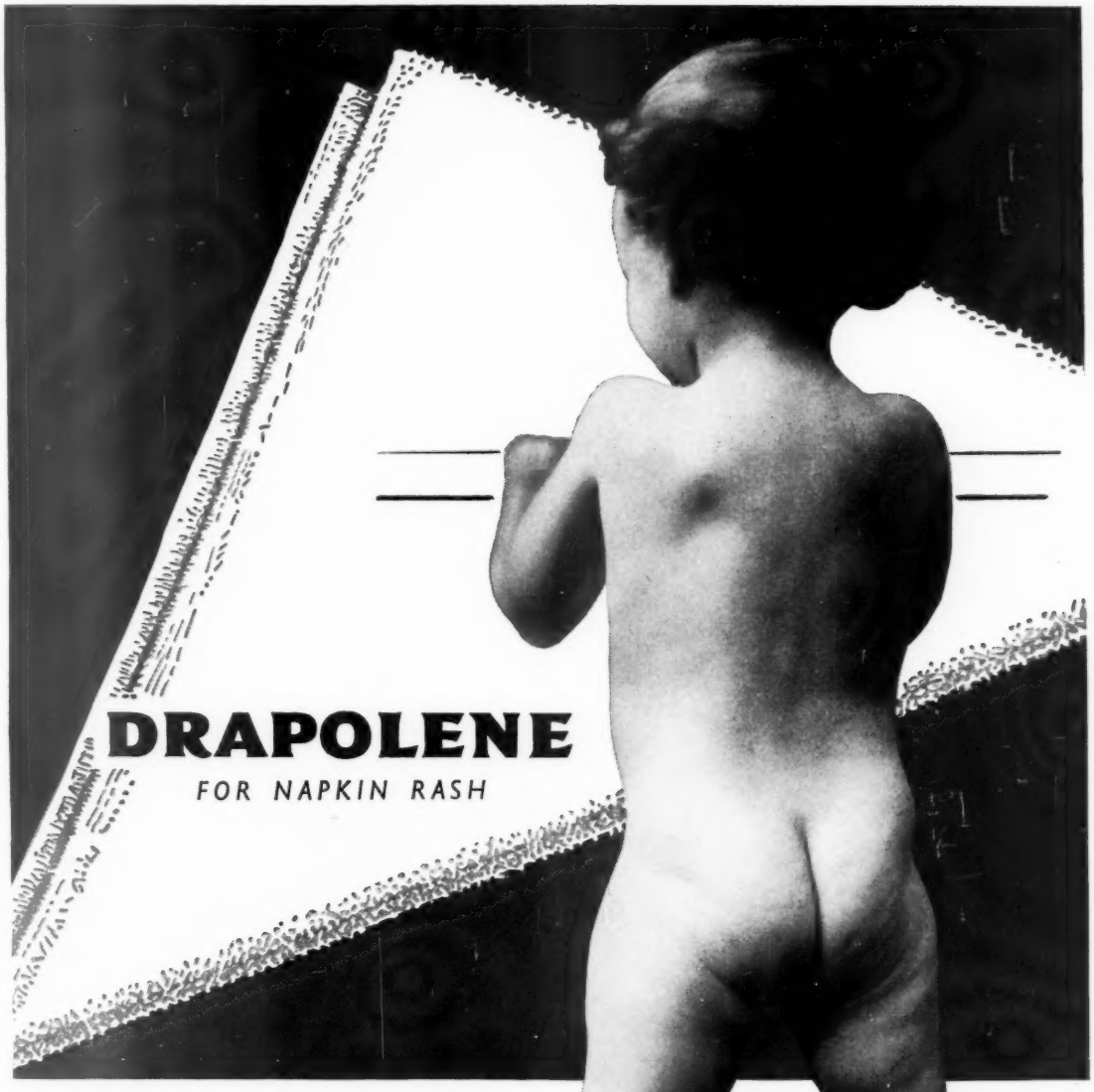

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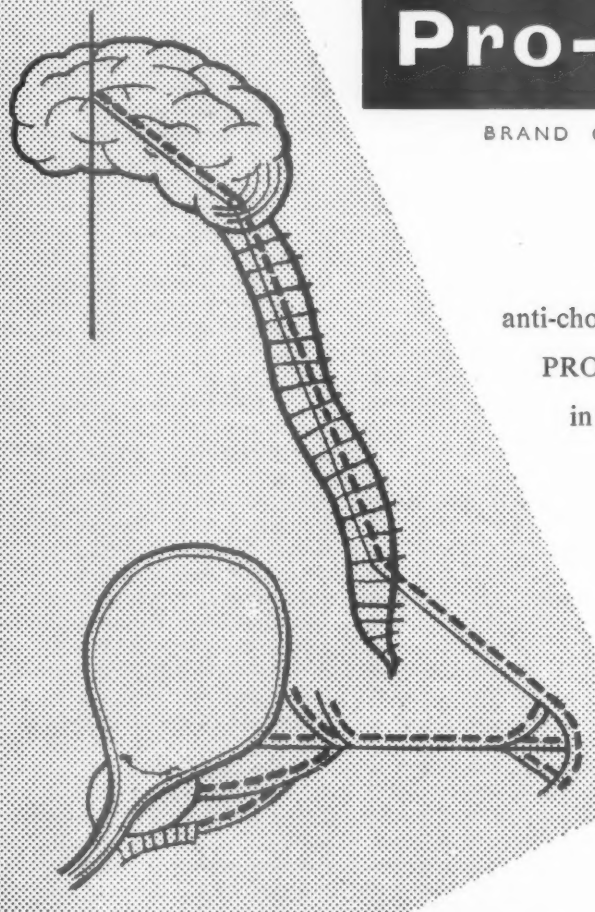

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SPINAL DYSRAPHISM

AN ORTHOPAEDIC SYNDROME IN CHILDREN ACCOMPANYING OCCULT FORMS

BY

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(RECEIVED FOR PUBLICATION OCTOBER 19, 1959)

Much interest has been shown in the pathology of the more gross developmental anomalies of the spinal cord and its coverings and in their clinical manifestations, most of which are not amenable to treatment. It has not been appreciated that lesser anomalies can also produce disabilities, that they can be diagnosed in life and that they can frequently be treated by surgery before the secondary effects have become severe and irreversible. Clinical experience over a number of years of the many children sent to orthopaedic clinics with various types of foot or lower limb defect led us to suspect the presence in some children of a spinal cord lesion responsible for a particular pattern of lower limb abnormalities. Such children were watched carefully and the development of their abnormalities and subsequent radiological and neurological investigations confirmed us in our belief that in a number of those children presenting at first with relatively trivial foot defects, there was an underlying spinal anomaly causing their troubles which might well be dealt with at an early stage, thus preventing further disability and perhaps improving such disability as had already occurred. We therefore decided to operate, at first upon those children whose abnormalities were beginning to increase seriously, and later, in the light of experience gained, upon all those in whom we had good reason to suspect the presence of a spinal lesion.

We now believe that we can identify with certainty a syndrome associated with and diagnostic of spinal dysraphism when there is an occult lesion affecting the spinal cord. By diagnosing this condition early we can undertake spinal surgery before severe deformity and disability of the lower limbs has occurred confident that surgery will be beneficial. The clinical manifestations are for the most part orthopaedic in that it is the lower limbs and feet which usually suffer. The treatment in the first place is principally in the field of neurosurgery since the removal of the primary cause, when it is possible, demands laminectomy and exploration around the spinal cord within the dura mater. Subsequent orthopaedic care will be needed only to correct established deformity if the diagnosis has been made late.

Spinal dysraphism is a term which has been applied to failure of complete development in the midline of the dorsal aspect of the embryo. The extent of this failure may be of mild, moderate or severe degree. The best known clinical form is meningomyelocoele which is an example of an overt lesion, but the lesion may not be visible on the surface nor make itself evident clinically. Spina bifida occulta is such a condition and is so commonly noted in routine x-ray investigations that it is regarded as a curiosity rather than as an entity with possible clinical implications. Ingraham and Lowrey (1943) have given an indication of the types of lesion to be found clinically, and other writers have described the particular lesions which interested them. None appears to have regarded these lesions as being of the same origin except Lichtenstein (1940), who revived the term spinal dysraphism and under this heading grouped disorders according to whether they manifested themselves as arising from cutaneous, mesodermal or neural derivatives of the dorsal median region of the developing embryo.

In this communication we are concerned only with those forms of spinal dysraphism which directly or indirectly affect the spinal cord and spinal nerves and our aims are to describe these lesions, to indicate the general pattern of the associated orthopaedic syndrome and to draw attention to the value of spinal surgery as a preventive measure when undertaken early.

The Lesions

Lesions affecting the spinal cord or cauda equina may be classified into three groups, those which produce a traction effect, those which exert local pressure and those which combine traction and pressure.

The Traction Group. In the growing child, there is a difference between the rate of growth of the spinal cord and that of the vertebral column. This is described as the ascent of the spinal cord within the vertebral canal, because the length of the latter, as the vertebral column grows, increases at a greater rate than the length of the spinal cord. At birth the distal end of the spinal cord is normally situated at or about the upper border of the body of LV.3 and at the end of growth, in adult life, is situated at the lower border of the body of LV.1 or the upper border of LV.2 (Streeter, 1919). Any lesion which prevents this ascent of the spinal cord will do so by fixing it at a definite level in the vertebral canal. In such circumstances the spinal cord or nerve roots or both will be stretched as the bone column grows and this stretching will produce injury either to the tracts within the spinal cord, or to the nerve fibres and indirectly to both of these by interfering with their blood supply. In all probability the commonest lesion of this type is diastematomyelia in which the spinal cord is bifid in part of its course. This is also the most easily diagnosed lesion when it is associated with a bone septum lying anteroposteriorly across the vertebral canal and transfixing the spinal cord. This bone septum can be seen on a plain x-ray film. A septum is, however, not always calcified; it may be fibrous and therefore not demonstrable by plain x rays.

Fibrous bands are also found tethering the spinal cord or cauda equina to the bone or skin directly or through attachment to the meninges. These may be associated with the fibrolipomata found in the pressure type of lesion. A tight filum terminale has often been cited as a similar traction lesion.

The Pressure Group. The best known type is the intrathecal lipoma, which consists of a fatty fibrous mass lying inside the dura mater. In some cases the fatty fibrous mass is entirely extradural; in others it may be extradural and intrathecal. Another type of pressure lesion occurs when a fibrous band constricts the lower end of the spinal cord situated at an abnormally low level (Léri, 1926). Occasionally, when the vertebral canal is already narrowed by inversion of one or more laminae, pressure may arise from increasing thickness of the bone with normal growth.

Within this group may also be placed those cases of congenital scoliosis resulting from hemivertebrae which develop paraplegia at about the age of 12 years.

The Combined Group. This group consists of a variety of lesions which incorporate external pressure by a fatty fibrous mass or by a transverse band with traction by some form of fibrous band attaching to the meninges, bone or skin.

Symptoms and Signs—Early Stages

Occult forms of spinal dysraphism are rarely evident at birth. At that time, the function of the spinal cord may not be impaired, but as the child grows, a dysraphic lesion will begin to have an effect, either by preventing the spinal cord from 'ascending' within the vertebral canal or by pressure from the increasing size of some abnormal tissue such as a lipoma. The effect, then, of a dysraphic lesion is a gradual interference with conduction in the spinal cord or its nerve roots, so that according to the site of the lesion there will be a gradual loss of sensation and a slowly developing weakness of some muscles leading to muscle imbalance and ultimately to deformity.

Symptoms. A child of any age is commonly referred because of a peculiarity of gait or because of distortion of one shoe, itself the result of a peculiarity of gait unnoticed by the parents. Sometimes a child attends because of poor posture associated with a short leg or because one leg has been noticed to be shorter and thinner than the other.

Pain is not a feature but there is occasionally a complaint of pain in one or more metatarsophalangeal joints which may be associated with a protective kind of gait. This is possibly the earliest evidence of this syndrome since in such cases at this stage there is no foot deformity.

Gait. The abnormality of gait, almost imperceptible early on, consists in an elevation of the first metatarsal head as though something like a drawing pin were underneath it, the great toe usually remaining flexed. Occasionally this is accompanied by adduction movement of the forefoot, but there is no evidence of abnormal function in the foot or toes when standing or when not bearing weight; voluntary actions are normal. In the course of review the peculiar action is more easily seen and the deformity which follows is quite obviously the result of this peculiar action; even so, the foot may still have a normal appearance at rest. If allowed to continue, the pes cavo-varus observed only when walking becomes fixed. The arch

FIG. 1a

FIG. 1b

FIG. 1c

FIG. 1.—Case 6. The deformity of the left foot in a moderately severe case. Right foot normal.

a Showing the inversion of the forefoot and the degree of cavus. Early clawing of the toes. Standing, bearing weight.

b Showing the inversion of the heel. The thinning of the calf is not well shown. Standing, bearing weight.

c Showing the shape of the sole and the shortening of the foot. Kneeling; the feet are not touching the background.

becomes higher, the forefoot more adducted and more inverted, and the toes become clawed. The result (Fig. 1 a, b and c) is not unlike the deformity seen in some cases of poliomyelitis and cases of relapsed club foot.

Lower Limbs. Examination of the lower limbs almost always reveals a shortening of one leg and foot, although it may be absent or very slight in the early stages. The affected leg is smaller in girth, both in the thigh and in the calf. The shortening of the leg rarely progresses to a final discrepancy of as much as 2 in. and it is usually much less, but the shortening of the foot becomes exaggerated by the cavo-varus and clawing of the toes. Peripheral circulatory deficiency is sometimes evident, showing as livedity or cyanosis.

In fully developed cases the combination of muscular imbalance and ischaemia produces fixed clawing with atrophy of the toes.

Nervous System. Reflexes are usually normal but may progress to an extensor plantar response and exaggerated, and later, absent knee and ankle jerks, as may occur in all progressive neurological lesions. Sensory changes have not been detected in younger children owing to their unreliable testimony, although some have exhibited trophic

changes. Older children manifest the usual alterations in sensation in the leg through dulling of light touch and hypersensitivity on deep pressure to total loss of sensation and also the characteristic saddle shaped area of analgesia over the buttocks and posterior surface of the thighs. We have not tested for loss of anal tone which other authors have found to occur (Jones and Love, 1956). Testing sensation in any child is difficult because the child will often give the answer which he thinks the examiner wants. The results are therefore commonly unreliable.

Back. There is frequently no superficial evidence of abnormality in the spinal column; occasionally a bifid spinous process may be palpable. The visible abnormalities in the back are cutaneous or subcutaneous; they are not present in every case and when present are not always associated with neurological deficit or foot deformity although these may develop later. They consist of the following:

(1) *Subcutaneous lipoma.* This is often associated with spina bifida occulta and exists as a diffuse soft mass of fat, usually over the sacrum.

(2) *Abnormal hair in the lumbo-sacral region.* Coarse hair several inches in length may be found which is maximal in the midline and exists from the time of birth. On occasion a silky down limited to a discrete area is found.

(3) *Angioma.* A superficial angioma may be found in or near the midline in the lumbo-sacral region.

(4) *Dermal dimples.* Skin depressions near to the midline with fixation of the epithelium to underlying layers may indicate the presence of a spina bifida.

(5) *Dermal sinuses.* Dermal sinuses near the midline may mark the outlet of a continuous fibrous or fistulous tract extending directly into the spinal cord but the cutaneous opening may be minute and may not be seen without a very close inspection of the back. These sinuses must not be confused with the common pilonidal sinus which has no connexion with the subarachnoid space and which is situated in the midline.

Progression and Later Stages

The majority of our cases have presented in the manner described or with the foot deformity already established. In the latter cases the mode of development of the deformity is no longer evident; there is already a pes cavo-varus with mobile clawing of the toes and except that weight is borne on the outer border of the foot no muscle can be seen to be overacting. The leg and foot are short and the arch of the apparently unaffected foot is sometimes a little high but within normal limits. When the foot deformity is established, the reflexes become abnormal and there may be sensory changes. With continued progression, sensation becomes increasingly impaired, trophic ulceration occurs and the deficient circulation becomes more obvious.

Another method of presentation is that of Case 2 (see Table) where the appearances of the lower limbs were similar to those seen in cases of myelocoele. We have not otherwise seen calcaneovalgus deformity developing after birth, but it is likely to occur probably where the spinal cord is affected at a high level and these cases are more likely to develop paraplegia. Other authors have mentioned such cases with paraplegia or weakness of the lower limbs and an unsteady gait.

A history of incontinence is unusual in early cases but bowel and bladder symptoms may develop later. There may be incontinence which cannot be diagnosed in a young child only just old enough to be expected to learn control (Case 2). Urinary incontinence of the type associated with a neurological bladder which empties itself only when fully distended is difficult to identify. Double incontinence with loss of bladder and bowel sensation may supervene in time.

In this description of the progression of lower limb abnormality it is clear that the syndrome is very similar to that occurring with spinal tumours except that the rate of progress in the latter is very much faster so that foot deformities have not time to develop. Paraplegia is likely to be the end result in both types of untreated case, although rare following spinal cord lesions associated with spinal dysraphism. The foot deformity which develops gradually over a long period in the dysraphism cases precedes the paraplegia.

Our experience of adult cases is limited and it appears that they are not often diagnosed. Their deformity has presumably been static for a number of years and they are unlikely to come for orthopaedic attention except for supply of surgical footwear. Those who develop trophic ulceration may be recognized if the clinician is aware of the syndrome, otherwise they are most likely to come to notice if they develop urinary or bowel dysfunction (Case X). Our personal adult cases were recognized by reason of attendance for supply of footwear, one of them having trophic ulceration.

Radiological Investigations

Apart from clinical examination and periodic review, the other chief investigation required is radiology. Every child (in the absence of a myelocoele) who shows a peculiarity of gait, poor posture associated with a short leg, a short and thinner leg,

progressive deformity of a foot, absent deep tendon reflexes or evidence of sensory impairment in the lower extremities, should have careful radiographic examination of the spine. Lichtenstein (1940) has pointed out that bone anomalies may be absent but it is our experience that plain films usually show congenital anomalies of the vertebral column such as spina bifida, which is the commonest abnormality, or hemivertebrae. A bone septum (diastematomyelia) may be shown. Spina bifida of even the slightest degree is almost always present in this syndrome but the bone abnormality is not necessarily at the site of the lesion, which may be situated some distance away as in Case 2.

Myelography is valuable for more exact diagnosis and for localization of the lesion but it should not be done lightly; its purpose is confirmatory. It will demonstrate space occupying lesions and obstruction to the flow of the opaque medium and if there is sufficiently clear definition of the filum terminale and nerve roots a myelogram may indicate the site of the conus medullaris. Occasionally the spinal cord may be seen to be held against the neural arches instead of being in its normal position lying against the vertebral bodies. Some traction lesions, however, are not demonstrated by myelography. Whilst screening it is necessary to examine the patient supine as well as in the classical positions. We have used myodil as the opaque medium; at lumbar puncture for its injection, cerebrospinal fluid is removed for examination and is usually found to be normal.

Diagnosis

At present the early case is not easy to diagnose confidently and usually the progress of deterioration has to be watched over a long period before the diagnosis can be established. There is a wide differential diagnosis and any history elicited from the parents must be considered with caution. A previous diagnosis of poliomyelitis may be suspect since it may have been applied *post hoc* to explain abnormality. A story of old injury likewise must not be accepted without further enquiry.

In the first place, the diagnosis depends upon the presenting symptoms. The peculiar gait suggests many conditions, a plantar wart, early hallux rigidus, injury to sesamoids underlying the first metatarsal head, foot strain, or too small a shoe. Pain, if present, may bring to mind March fracture, early hallux rigidus, trauma, foot strain, osteochondritis of a metatarsal head or of the navicular, or lumbar nerve root irritation.

The cases of short foot and leg of the variety for which no cause is found are distinguishable from those due to spinal dysraphism in the course of long term review by the foot shape, function and the gait, which continue to be normal. Other possible causes of a short foot and leg are old bone infection, previous fracture, poliomyelitis and hemihypertrophy or angiomatosis of the other limb.

Disease of the nervous system must be excluded, e.g. neurofibromatosis, tumour of the cauda equina, Friedreich's ataxia, the distal (Gower's) type of myopathy, peroneal muscular atrophy, polyneuritis and cerebral palsy.

In the late case, the limb deformity and the neurological deficit make the diagnosis straightforward.

Treatment and Results

Excluding cases of diastematomyelia with a bone septum evident on a plain x-ray film that ought to be operated on at once, the only treatment possible in the early stages is a passive correction of the shortening by the use of raising on the shoe, with or without irons. This treatment is rarely effective for any length of time. When the presence of a neurological deficit has been established, laminectomy should be performed after myelography. Surgical exploration of the vertebral canal, including opening the dura to permit inspection of the spinal cord, is intended to remove the cause of the disability by releasing the anchoring of the spinal cord or by excising the cause of pressure. The results expected are not that the lower limbs will return to normal, nor that previous incontinence will be cured, although these things may happen if the case is dealt with early enough, but that there will be no further deterioration nor increase in the lower limb abnormalities and deformities. The changes which have taken place in the spinal cord and nerve roots may be irreversible so that recovery cannot occur. The operation is essentially preventive. Orthopaedic treatment will be necessary to correct the established foot deformity and residual muscle weakness. After removal of the primary cause of muscle imbalance, full use can be made of normal function and growth in the correction of any postural foot deformity. Without removal of the primary cause, orthopaedic treatment may temporarily correct a postural deformity but is ineffectual except as a short term expedient.

Illustrative Cases

In the Table we present a summary of our first 16 fully investigated cases. There are many other cases under review some of which are awaiting myelography. The cases in the summary are given in order of myelography and some, which are not cases of the syndrome described, have been in-

FULLY INVESTIGATED) ERS O

Case	Sex	Date of Birth	Date First Seen	Syndrome	Neurology†						Sensati
					K.J.		A.J.		Plantars		
1	F	18.12.46	17.12.56	Poor circulation lower limbs; right foot slightly smaller than left	++	+	+	+	?	F	? sep
2	M	19.5.53	12.1.55	Dragging inverted left foot and everted right foot; progressive paralysis of lower limbs	+	−	−	−	E	E	Abnorm sing sing
3	F	5.3.45	7.9.55	Left pes cavus with clawing and dropping of forefoot; left leg short ½ in.; right foot normal	+	+	+	+	F	−	Norma ne
4	F	8.8.45	12.2.57	Inverting left foot only when walking, distortion of shoe, progressive cavo-varus; right foot normal; legs equal length	±	±	−	−	F	F	Norma le ; na ior
5	F	11.11.46	23.7.47	Originally clawed outer toes left and severe valgus both feet; not seen 1951-55 and then left foot smaller than right; progress: left cavo-varus and clawing; poor skin circulation; sacral naevus and excess hair	+	+	+	−	F	−	? ed s
6	M	21.12.46	9.6.55	Left cavo-varus; left foot shorter than right; left leg ½ in. short; sacral hairy patch	+	+	+	+	F	E	Norma bif ral
7	F	30.8.50	1.11.54	Right foot smaller than left since birth; developed mild cavo-varus; sacral hair	−	+	−	+	E	F	Norma bifi rae)
8	M	21.8.52	4.11.57	Short left leg and foot; pes cavus R. and L. worse with progressive increase of varus in left; increasing weakness of left foot; falling over frequently	+	+	++	++	?	E	? spi l
9	F	18.11.47	17.2.58	Mild pes cavus at birth; developed pain left foot with increasing cavo varus and hypersensitivity and impairment of joint sense; left foot smaller than right; legs equal length; weakness dorsiflexors left foot	+	++	+	++	F	F	Abnorm ate
10	F	30.8.45	14.11.51	Left club foot treated at birth; short right foot and leg developed and increasing cavo-varus of both feet, later left leg was shorter	−	−	−	−	−	−	Trophic ud sp loss of sen in both fe
11	M	2.2.56	9.2.56	Bilateral club feet with full correction obtained by age of 4 mths; persistent overaction of Tib. Ant. with progressive increase in cavo-varus deformity starting at age of 18 mths; lower limbs becoming a little spastic	++	++	++	++	E	E	? pin
12	M	17.4.50	7.9.50	Left leg and foot smaller than right from birth; left foot originally very valgoid but aet. 5 yrs started developing cavo-varus; sacral hair	+	−	+	−	F	?	Abnorm ive cru
13*	F	26.6.46	1.11.54	Since infancy small right foot; sacral fat pad; developed right claw toes and cavus with increasing cavo-varus; left foot mild cavus	−	+	−	+	−	−	Abnorm bifi lu is
14	M	13.10.54	13.5.58	Persistent inversion left foot; left foot and leg short; pes cavus developing in left foot	+	+	+	−	F	E	? bifi l la
15	F	11.12.46	8.3.55	Rapidly increasing left pes cavo-varus; short left foot; legs equal length	+	+	+	−	F	E	? d sp
16	F	5.7.48	15.7.58	Short right foot and leg, with early right pes cavus; patch of hair over lower thoracic and lumbar region	−	+	−	+	?	F	Abnorm spi ano raph

* Case referred to us by Mr. J. K. Stanger and Dr. Christine Cooper.

† *Neurology:* + = present − = absent

ED ERS OF SPINAL DYSRAPHISM

Sensation	Survey Radiograph		Myelography	Comment
?	septum LV.2; spina bifida LV.3-SV.1	30.3.57	Diastematomyelia	*Laminectomy* (4.4.57) Bone septum at LV.2/3 level excised; diastematomyelia 1·9 cm.; conus at lower border LV.4
Abnormal	al spina bifida LV.4 and 5 and SV.1; sing interpedicular widening at LV.1 ting enlarging tumour	6.11.57	Total block preventing flow to LV.1	*Laminectomy* (11.11.57) Transverse pressure band from pedicle to pedicle at LV.1; spinal cord was markedly enlarged at and below this level, probably the result of gliosis
Normal	ne abnormality	12.11.57	No abnormality demonstrated	Deformity not progressing after tendon transplants in foot; right foot normal
Normal	le anomalies of whole spine; tomo- narrowing of vertebral canal anteroiorly by laminae at LV.5	12.12.57	Filling defect left side of LV.5 level	Parents refused operation; left foot deformity slowly developing
?	d spina bifida LV.2—sacrum	31.1.58	Enlarged filum terminale and abnormally caudal conus	*Laminectomy* (31.3.58) Traction band at LV.3 extra and intra-dural attaching to filum terminale and left S.1 nerve root and holding spinal cord posteriorly; conus at caudal border of LV.3
Normal	bifida LV.5-S.1 with anomalies of al bodies	25.4.48	No abnormality demonstrated	*Laminectomy* (9.6.58) Traction band, extradural, at LV.5; absence of extradural fat in this area and adherence of ligamentum subflavum to dura; conus at caudal border of LV.3
Normal	bifida LV.4 and S.1 (only four lumbar rae)	30.4.48	Diastematomyelia; conus abnormally caudal	*Laminectomy* (16.6.58) Fibrocartilaginous septum LV.4; ligamentum subflavum adherent to dura in this area with absence of extradural fat; diastematomyelia limited to area of septum
?	spina bifida at LV.5 and greater degree l	14.5.58	No abnormality demonstrated; some extrathecal myodil	Undiagnosed
Abnor	ate spina bifida SV.1	23.6.58	No abnormality demonstrated	Physical signs improving; undiagnosed
Trophic u loss of sen in both fe	d spina bifida TV.9—sacrum	16.7.58	Diastematomyelia; conus situated abnormally caudal	*Laminectomy* (22.9.58) Bone septum LV.2; conus not seen, but situated below mid LV.4
?	pina bifida LV.5 and more severe at	3.9.58	No definite abnormality demonstrated but theca lay away from the vertebral bodies	Probably cerebral palsy but undiagnosed; not club foot relapsing in the usual manner
Abnor	ive spina bifida of whole lumbar spine crum	19.9.58	No definite abnormality demonstrated	Under review; foot deformity worse; awaiting laminectomy
Abnor	bifida and gross anomalies mid and lumbar, with some lower lumbar is	6.10.58	Diastematomyelia (minute); conus abnormally caudal	*Laminectomy* (9.10.58) LV.3 level, intradural band holding spinal cord posteriorly and rotating it; the spinal cord was bifid immediately cranial and caudal to the attachment of the traction band; the conus lay distal to the level of LV.3 caudal margin
?	bifida of LV.5 with caudal extension t lamina of LV.4	12.11.58	Appearances not understood; conus situated abnormally caudal	*Laminectomy* (24.11.58) Traction band LV.5 lamina to dura and transverse pressure band at LV.4-5 level; conus tip at lower margin of body of LV.4
?	d spir bifida LV.3 to SV.1	3.12.58	No abnormality demonstrated; conus abnormally caudal	*Laminectomy* (25.5.59) Transverse pressure bands at LV.5; absence of extradural fat in this area; conus not seen, probably at caudal border of LV.3
Abnor	spina bifida lower thoracic, upper rand LV.5; conus at about LV.3 level; raph: one septum at TV.9	28.1.59	Diastematomyelia	*Laminectomy* (2.2.59) Diastematomyelia extending about 7 cm.; the cords were adherent to the bone septum

t — = diminished ++ = exaggerated. *Plantar responses:* E = Extensor F = Flexor ? = Equivocal — = Absent.

cluded because we thought at the time that the lower limb abnormalities might possibly be ascribed to a lesion of the spinal cord and also because they demonstrate some of the difficulties of differential diagnosis. No fully investigated cases have been excluded.

All of the 10 cases submitted to laminectomy have had demonstrable lesions at operation although the mechanism by which the lesion produced its effect is not clear in every case. In none of these cases has there been any further deterioration and most have improved in an encouraging way. Myelography demonstrated diastematomyelia in six cases and a total block to flow of myodil in one. In the three other cases myelography showed no abnormality in one and in the other two the termination of the spinal cord could be seen to be abnormally caudal.

Four cases are described below in detail, three from our personal series, of which Case 5 had a traction lesion, Case 2 a pressure lesion and Case 14 a combined traction and pressure lesion. Case X (an adult) is given as an example of spinal dysraphism presenting with urinary symptoms resulting from a pressure lesion. This patient was not one of our personal series. He was seen in consultation before operation and is reported here with permission of Mr. Keith Yeates, Dr. John Walton and Mr. John Hankinson.

Case 1 of the series has been reported and discussed elsewhere (James and Lassman, 1958).

Case 5. Female, aged 11 years. This child was first seen at an orthopaedic clinic in March, 1947, when she was 4 months old because the left foot was smaller than the right and the fourth and fifth toes were flexed. The deformity of the toes was treated by strapping and manipulations. In September, 1950, the toes were operated on to correct the deformity. She was not seen between June, 1951 and December, 1955, when she came under our care because she was distorting her footwear. Her left foot was much shorter than the right and there was a tendency to inversion and equinus with dropping of the forefoot. She had a sore on the back of the tendo-achilles and an unpleasant callous under the fifth metatarsal. By July, 1957, the foot condition had altered; the right foot was normal, the left foot was very short, rather high arched with hyperextension activity of the great toe. The muscles of the ankle, foot and toes were functioning, but in voluntary use the invertors overacted. There was still a callous under the fifth metatarsal head. The skin of the left calf was cyanotic and became purple in cold weather and the circulation in the foot was poor. The left leg was at least ½ in. shorter than the right. The left ankle jerk was absent. A pigmented patch to the left side of the sacrum and excessive hair in the lumbo-sacral region were found on examination.

Radiographs of the lumbar and sacral spine demonstrated a marked spina bifida in the lumbar region from LV.2 downwards and also in the upper sacral region (Fig. 2).

Myelogram outlined a midline structure in the terminal theca which was wider in diameter than one would expect for the filum terminale (Fig. 3). This was thought to be possibly anchoring the cord as the conus medullaris lay at an abnormally low level. With this evidence and the clinical history and findings, spinal exploration was considered to be justified.

At operation when the laminae had been superficially exposed, a fatty fibrous mass was found between the laminae of LV.4. This mass was isolated by laminectomy of LV.3 and could be easily lifted off the dura to which it was attached by a fibrous band. The band, accompanied by an artery, passed from the deep surface of the fatty fibrous tissue to the dura, continuing from the deep surface of the dura to the very large filum terminale and to the left first sacral nerve root within the dura. It was approximately ½ in. in diameter and 1½ in. in length and was holding the cord towards the neural arch and away from the vertebral bodies (a state not evident in the myelogram). The spinal cord fell to normal position when the band was divided, but was not seen to shift cranially with the release of tension. The conus lay at the level of the caudal border of LV.3.

The post-operative course was uneventful.

When seen 10 months after operation, the circulation in the left leg was normal and the blue and purple discolouration of the calf no longer occurred. The reflexes

FIG. 2.—Case 5.—Antero-posterior survey view of the lumbo-sacral spine showing marked spina bifida in the lumbar region from LV.2 downwards and also in the upper sacral region.

FIG. 3.—Case 5. Myelography demonstrates in the terminal theca a midline structure which is wider in diameter than would be expected for the filum terminale. The appearances suggest that the spinal cord is anchored down and that the conus medullaris lies at an abnormally low level.

were unchanged. The shortening of the left leg was a little more than 1 in. There was subjective sensory improvement in the foot, in that she could feel, when she put her foot to the ground, a sensory deficit of which she had been unaware before operation. There was increased muscle power and the foot was used in a plantigrade manner, no longer being inverted when walking.

Case 2. Male, aged 4 years. This boy was referred to an orthopaedic clinic in January, 1955, at the age of 20 months because he was not walking on his own. He was healthy and was a full-term baby without neonatal complications. On examination, when he attempted to walk holding on to the furniture, he inverted his left foot and everted his right. When in a standing position, the left foot showed a voluntary tendency to adduction and inversion of the forefoot which the mother had first noticed two months previously. Until then, she had thought that the boy's feet were quite normal. He was not obviously spastic in the left lower limb, but his gait suggested this possibility. He was given irons to wear and slowly gained in strength to be able to walk on his own. Sensation in the legs seemed deficient at about 2 years of age; his lower limbs at this time resembled those of a child with a myelocoele.

He was in hospital for 10 weeks from February to April, 1956, owing to trophic ulceration of the right third, fourth and fifth toes possibly induced by a hot water bottle. During this period, whilst the toes healed very slowly the deformities of his feet became more severe and more fixed in spite of splintage. By April, 1957, his lower limb power was deteriorating rapidly and he was hardly able to walk barefoot. On October 31, 1957, he was admitted to hospital for investigation, by which time he was unable to walk without assistance even with short irons and boots. He had very little voluntary power of the knees and feet but quite good power of hip movement. It was difficult to determine his degree of sensory loss but he had analgesia to pin prick on the back of the thighs and in the sacral region. The left knee jerk and both ankle jerks were absent and the right knee jerk was just present; both plantar responses were extensor. He had always been doubly incontinent, having no idea when his bladder or rectum were full.

Radiograph of the dorsal, lumbar and sacral spine showed spina bifida of LV.4, LV.5 and upper sacral region with widening of the interpedicular distances with flattening of the pedicles most marked at the level of LV.1 but extending from TV.11 to LV.2 in a lesser degree. The lateral view showed that the posterior aspects of the bodies of these vertebrae were concave. The flattening of the pedicles suggested to the radiologist that the lesion was an expanding one, but he did not think it excluded congenital origin.

Myelography was performed and the myodil flowed upwards as far as the level of the body of LV.1 where a complete block to the upward flow was demonstrated. The radiologist was unable to detect any negative shadow of the spinal cord but several half shadows were present in the myodil suggesting either a gross anomaly or a gross displacement of the cord, probably the former. The myodil passed laterally on both sides into the exit foramen between LV.1 and LV.2 in a manner which suggested a congenital anomaly. The upper border of the myodil in the head down position showed no typical shape but rather an irregular contour in the lateral view.

At operation on November 11, 1957, the spinal cord from TV.12 level caudally to just proximal to the conus was enlarged and white in colour; an extradural fibrocartilaginous band compressed it transversely at the level of the pedicles of LV.1. The cord pulsated cranial to this band and at the conus but not in between, and the band was clearly restricting the flow of cerebrospinal fluid from above downwards. After removal of the band the cord beneath began to pulsate and there was a clear flow of the cerebrospinal fluid downwards. The enlargement of the spinal cord appeared to be due to a congenital abnormality and was not in any way cystic. Microscopy revealed the band to be composed of dense acellular fibrous tissue structurally resembling a ligament.

After operation the boy developed a cerebrospinal fluid fistula and continued to drain cerebrospinal fluid in very large quantities despite further attempts to close the gap. Ventricular drainage became necessary to allow the back to heal and the quantity of fluid discharged through the drain, together with the difficulty of controlling the flow from the fistula, suggested some abnormality of cerebrospinal fluid production. There was no other evidence, internal or external, to suggest

that there was an associated Arnold-Chiari malformation.

After discharge from hospital on January 30, 1958, the strength of his lower limbs developed quite rapidly to begin with but he could not walk without assistance for nine months after operation. Subsequently he began to walk without sticks, wearing a caliper on the right leg. Fourteen months after operation the foot deformities were unchanged; he still lacked voluntary power in the evertors of the left foot and in the invertors of the right, but there has been some recovery in the right calf muscles. Lower limb sensation was difficult to assess but five months after operation his right plantar response was flexor and 12 months after operation a flexor response was obtained on the left side.

His mother stated that approximately one month after discharge from hospital, the boy, for the first time, began to know when his bowels were going to work and after this time he rarely dirtied himself, provided he was near home. As regards micturition, she thought the boy had some feeling but since he wore either a urinal or a napkin he made no effort to control himself.

FIG. 4.—Case 14. Antero-posterior survey view of the lumbo-sacral spine. The laminae of LV.4 extending caudally exhibit a curious apparently curved bony ridge crossing the spinal canal at LV.4/LV.5 level.

Case 14. Male, aged 4 years. He was referred to an orthopaedic clinic at the age of 3 years 6 months, because he had been walking with his left foot inverted since the age of 18 months. This tendency was evident in the clinic but there was no real abnormality of the foot apart from slight shortening as compared with the right foot. Examination showed a slight (less than ½ in.) shortening of the left leg; normal right leg reflexes, an absent left ankle jerk and a left extensor plantar response. The left lower limb felt spastic on passive movement.

During the next five months the left foot rapidly developed cavo-varus. The back appeared normal. There was no evidence of bladder or bowel disturbance and the reflexes were unaltered. Sensation was not tested.

Radiographs showed spina bifida of LV.5 and the laminae of LV.4 extending caudally made a curious apparently curved bony ridge crossing the spinal canal at the level of LV.4/5. The interpedicular distance at the lumbo-sacral level was increased (Fig. 4).

Myelography showed no definite abnormality, but suggested that the conus medullaris lay almost at the level of the lumbo-sacral articulation. There were some linear translucencies which could not be satisfactorily explained.

Exploration was decided upon, in view of the neurological deficit in the left lower limb, the rapid development of cavus in the left foot, and the curious myelographic appearances.

At operation the spinous process of LV.4 was found to be expanded on the right side and the right lamina of LV.4 was continuous with that of LV.5. At the level of the pedicles of LV.4 an extradural transverse band firmly adherent to the dura was constricting the spinal cord. Immediately caudal to this transverse band and partly attached to its caudal edge was a cylindrical band 1·0 cm. long with five webbed digital prolongations, which were firmly fixed at their anterior ends to the dura and at their posterior ends to the deep surface of the fatty fibrous tissue which filled the gap. This traction band ran obliquely from the midline of the dura in a caudal direction towards the right side in such a way that the whole spinal cord was probably held posteriorly to the right. The traction band was excised, and the transverse band was divided when the dura was opened to expose an apparently normal spinal cord with the conus lying caudal to the transverse band at the level approximately of the intervertebral disc between LV.4 and LV.5. The dura was closed without difficulty but for two or three days post-operatively there was a fluid fistula which healed without further interference. Microscopy of the traction band showed very dense fibrous tissue.

Three months after operation there was no change in the physical signs. At six months, the reflexes were unaltered and there had been no change in the degree of cavo-varus as compared with the state before operation; progression had ceased.

Case X. Male, aged 26. Up to the age of 11 years he had suffered incontinence of faeces and when aged 18 years a small swelling had been removed from over the coccyx. He had begun to experience increasing difficulty in passing urine for two years before his admission to hospital for investigation. Whilst in hospital and shortly after a myelogram, he developed acute retention of urine.

Examination showed sensory loss around the anus and perineal region and on the buttocks in the distribution of the fourth sacral and first coccygeal segments;

there was no abnormality in the lower limbs. Survey radiographs revealed spina bifida of the lower sacral segments S3-S5 which was remarkably wide at S4 and S5.

At myelography, the myodil flowed downwards to the level of the S3/S4 segments. In the supine position the myodil column divided into two lateral columns at the level of the lower border of S5, leaving an oval shaped defect in the outline of the myodil. In the lower lumbar and upper sacral region the appearance of the myodil column suggested that the spinal cord was extending to a very low level.

At operation Mr. Hankinson found a lipoma attached to the skin in the region of the sacral bone effect. The lipoma passed through into the vertebral canal and was continuous with the dural sac and within the dura it was firmly attached to the spinal cord. The spinal cord was of normal thickness and extended to the lowermost portion of the sacrum; the spinal nerve roots passed horizontally to escape through their respective intervertebral foramina in the manner usually seen only in the early stages of human foetal development. The attachment of the lipoma at the periphery of the bone defect was freed and the dura left open and covered with gelfoam. Spontaneous micturition slowly returned and two weeks after operation catheterization was no longer required. The difficulty with micturition has continued to decrease.

Discussion

The picture of this syndrome and its causative lesions which we have endeavoured to draw is based on information from the literature and on a personal series of 16 cases completely investigated and submitted to myelography and more than 20 clinical cases under review and as yet unproven. All these are children. The unproven cases do not include the many cases seen which for no known cause have one leg shorter than the other and a small foot, a combination which is remarkably common in children's orthopaedic practice. Many cases produce a foot deformity which does not progress and, not having developed a neurological deficit, do not appear to justify full investigation and laminectomy. Some of these cases no doubt would have a lesion demonstrable on myelography and surgical correction of the lesion would prevent the full development of deformity but since myelography is dependent on the introduction of a foreign substance into the subarachnoid space it is not an investigation to be carried out without considerable forethought and good reason. Indeed, our policy has been to undertake myelography only if we expect to proceed to operation when the myodil will escape. We have used myodil in our cases and it has been the material used as a routine by the Department of Neuroradiology for a number of years. So far there has been no complication occurring from its use and as we gain further experience with myelography we may be able to change our criteria and use it more frequently. The technique of myelography and the understanding of the radiograph appearances need expert management and we are most grateful to our colleague, Dr. Gordon Gryspeerdt, for his skill in this technique and his guidance in interpretation.

It is becoming apparent from our operated cases that some of the traction lesions may give little or no evidence of their presence by myelography. Case 5, reported above, is an example. The myodil column must be examined throughout the whole theca from the cervical region down to the sacrum; Shorey (1955) has reported a case with lesions at two levels, thoracic and lumbar.

If a myelogram fails to demonstrate a lesion which is in fact present, it fails also to provide a localization of the site to be approached surgically. A normal myelogram thus deprives the surgeon of a valuable piece of information since the lesion affecting the spinal cord may not lie in the immediate vicinity of the bone defect. In some of our cases with a normal myelogram we have been able to operate and find a lesion only because the pattern of spina bifida resembled that occurring in a case previously explored and thereby suggested the likely site and the type of lesion to be anticipated.

All our investigated cases except one have spina bifida occulta, varying in degree from the barely noticeable to the very extensive. The one case with no bone anomaly shown on a radiograph had a normal myelogram; the short leg and pes cavovarus show no further deterioration in the last 12 months and there is no neurological deficit. This child has not been operated on.

As we have already pointed out (James and Lassman, 1958), there is no published information about the normal level in the vertebral canal of the conus medullaris during the years between birth and full growth although we have post mortem evidence suggesting that the ascent of the spinal cord is normally completed by the end of the fifth year of life. Where myelography can demonstrate the level of the conus and when this can be regarded as abnormally caudal, there can also be assumed to be a traction lesion which should be dealt with surgically. Many of these traction lesions will show no other abnormality on myelography and they are the most difficult to diagnose and to localize. Tomography can be of assistance in some cases, notably those with a bone septum in diastematomyelia and those with inversion of laminae where the demonstration of the size and locality of bone anomaly assists the surgeon in the planning of the

operation which must, of course, involve as few laminae as possible. Only two of our cases needed excision of four pairs of laminae; the remaining eight had three pairs removed.

Pain has not been a factor in the symptomatology of our cases, nor has the spasticity reported by other writers, and this is possibly because we have been able to see our cases at an earlier stage in their history. Neither has ataxia in the form of clumsiness and unsteadiness been evident (except in Case 2), but it is obviously likely to occur at a later stage. Low back pain or stiffness occurring on getting up in the morning and passing off with activity has been referred to by other authors but has not been complained of in our series. The two most important early clues to indicate a possible lesion affecting the spinal cord or cauda equina are either a short leg and foot or a circulatory defect of the skin of the lower limb (as in Cases 5 and 2) of the type seen following poliomyelitis and associated with spina bifida cystica (see also case reported by James and Lassman, 1958).

We wish to stress again the importance of investigating any statement by the parents as to causation of the deformity. Just as other clinicians have done, we have seen many cases where a deformity has had to be considered as due to poliomyelitis because no other cause appeared to be likely; this diagnosis has naturally been passed on to the parents in spite of the absence of any other real evidence of this infection in the past. Injury also has often been advanced by the parents as their own idea of the cause; it is surprising how many children have been dropped in infancy. One adult found to be affected attributed the foot deformity to an injury caused at the age of about 1 year, when her forefoot had caught under a door. She and her family had been satisfied to accept this explanation ever since. Her left foot was normal but the right foot had markedly diminished sensation, pes cavus, clawed atrophic toes and trophic ulceration. Her right leg was $\frac{1}{2}$ in. short. She had two hairy patches on her back and radiographs showed congenital anomalies of the lower lumbar spine and sacrum. The few adult cases we have seen have not been investigated to the extent of myelography. Their deformities, neurological deficits and trophic lesions have been in existence too long to be likely to benefit by laminectomy. They have been treated as conservatively as possible in the same way as cases of spina bifida cystica.

It is clear that the types of abnormality associated with occult spinal cord lesions are similar to those associated with overt spinal cord lesions, although the severity of the physical disability in the latter is usually much greater. The essential difference between the two types of lesion of the spinal cord is that the occult lesion is usually extrinsic, whereas the overt lesion is an intrinsic lesion of the spinal cord itself. The latter is therefore much more severe and results not only in failure of spinal cord development but also in failure of formation of normal tissues which should be developing synchronously with the spinal cord. The extrinsic lesion occurs slightly later in foetal development there may be no associated failure in other tissues and its principal effects occur with growth of the child after the associated tissues have been formed; the subsequent abnormalities therefore develop gradually and later in life. As has already been indicated in the syndrome we have described, the established deformity of pes cavo-varus resembles a type of relapsing club foot. If the extrinsic lesion of the spinal cord were to have an effect *in utero*, the pes cavo-varus would possibly have the appearance at birth of a typical club foot because the muscle imbalance would have started earlier and would have been able to advance more rapidly. After birth there are restraints upon this muscle imbalance by the establishment of coordinating reflexes and by the decreasing plasticity of the bones of the foot which provide a mechanical obstruction.

In this communication we have made statements which are based on facts and experience; we have avoided theory as far as possible, but as we continue our clinical and surgical investigations we believe that it may be possible to classify some types of foot deformity as being caused by occult spinal cord lesions. Some cases of club foot are associated with meningomyelocoele but the aetiology of other cases is still unknown, and it seems possible that some of the other cases which relapse repeatedly and necessitate local surgery may be due to an occult spinal lesion of the type which we have described here.

The well known association of pes cavus and spina bifida occulta may possibly be now explained but all cases of pes cavus do not necessarily fall into this class and there is obviously need for a reclassification by specifying with greater care the exact form of the pes cavus.

Sufficient information has been obtained to conclude that it is possible to diagnose these cases early and to perform preventive laminectomy without waiting for foot deformity to become fixed. Case 5 demonstrates that with such early procedure muscle balance can become normal or nearly so. Altered bone shape in the older child resulting from abnormal muscle action cannot return to normal but in the very young child almost complete recovery

n this respect may be possible with the return of normal muscle function.

Summary

The purpose of this communication is to emphasize that many types of spinal lesion which have been reported individually are different manifestations of spinal dysraphism and that it is important to recognize their common pattern of symptoms and signs so that an early diagnosis can be made and further deterioration and disability prevented by surgical removal of the cause.

The spinal lesions are classified in three groups, as traction lesions, pressure lesions and combined (traction and pressure) lesions. One case of each type of lesion, proved by operation, is described.

The symptoms and signs facilitating early diagnosis in childhood are discussed. The commonest and earliest evidences are shortening of one foot and leg or circulatory deficiency of the skin of the legs.

The progression of the syndrome by stages to severe neurological deficit, to deformity of the lower extremities and possibly to paraplegia is also described.

The necessity for myelography as a diagnostic procedure is indicated and its uses are discussed. It is valuable as a preliminary to laminectomy in demonstrating not only the nature of the lesion but also its site. A normal myelogram does not exclude the presence of a lesion. Laminectomy as a method of treatment can be expected only to halt the progressive deterioration. In some cases, however, partial recovery will occur, but such a possibility can only be hoped for and the main purpose of operative treatment is to prevent further disability.

We are indebted to Dr. Gordon Gryspeerdt, Neuroradiologist and to Dr. Douglas Whitby, Anaesthetist, for their most helpful collaboration in the diagnosis and treatment of our patients and also to our colleagues, Dr. George Davison and Dr. Christine Cooper, in the Paediatric Department of the Newcastle General Hospital. The photographs and reproduction of the x-ray films were produced by the University Department of Photography, King's College, Newcastle upon Tyne.

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CORTICAL ATROPHY OF THE BRAIN IN INFANTS ASSOCIATED WITH FAILURE TO THRIVE

BY

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(RECEIVED FOR PUBLICATION SEPTEMBER 4, 1959)

Infants may fail to thrive for a variety of reasons. When recognized causes such as congenital abnormalities, infections, defective intake and absorption, metabolic and endocrinal disturbances have been excluded, there still remains a group in which no satisfactory explanation is readily apparent. One cause which may account for some of these marasmic infants, and which does not appear to have been previously recorded, is cortical atrophy of the brain. Attention was drawn to this possibility by finding a hemiplegic infant who would not gain weight. An air encephalogram (A.E.G.) revealed cortical atrophy of the brain. Subsequently A.E.G.s were done on other infants, even if they had no clinical signs of damage to the nervous system. In all of them, unless stated to the contrary, the urine, chest radiograph, Mantoux test, Wassermann reaction, blood urea and serum chemistry were normal. Air encephalograms were only done if, after two months of adequate diet in hospital, there was no satisfactory reason found for the failure of these infants to gain weight.

Lumbar A.E.G.s were done under sedation with seconal and largactil. Spinal fluid was replaced by an equivalent volume of air. The total volume of air varied from case to case, but in no child was an excessive amount injected, nor was there any increase in intracranial pressure as judged by bulging of the fontanelle during or following the procedure. No ill effects following A.E.G. were seen in any of the infants.

Case Histories

Case 1. V.W., aged 4 months, was admitted on November 28, 1955, weighing 6 lb. 7 oz. Birth weight was said to be 3 lb. 3 oz. The only abnormal physical signs elicited were a mild right spastic hemiparesis and a head circumference of 13·25 in. A radiograph showed two well-developed centres of ossification in the carpal bones. Eleven weeks after admission the child weighed 6 lb. 15 oz. A.E.G. showed some ventricular dilatation and excessive cortical air suggesting atrophy. By the age of 2 years 9 months the child had grown fairly well, her head circumference was 17·75 in., but the hemiplegia was marked and she had difficulty in speaking.

Case 2. C.P., aged 6 weeks, was admitted on February 7, 1956, weighing 7 lb. 6 oz. Labour and pregnancy were normal. The infant sucked poorly, vomited intermittently and failed to thrive. Fifteen weeks after admission she weighed 7 lb. 5 oz. A barium swallow and meal revealed nothing abnormal. She was somewhat slow in her development but had no abnormal neurological signs. An A.E.G. at the age of 6 months was only contemplated because of the findings in Case 1. It showed excessive cortical air compatible with atrophy.

Case 3. S.G., aged 7 months, was admitted on March 17, 1956, weighing 9 lb. 6 oz. The pregnancy had been normal but the infant had been born by breech delivery. The child sucked poorly. She had a bronchopneumonia and it was noted that she could not sit. She was re-admitted at 10 months, weighing 11 lb. 10 oz., because of vomiting and failure to thrive. A barium meal showed a hiatus hernia. Vomiting improved somewhat on medical treatment but at a year she still could not sit unsupported. There were no abnormal neurological signs except occasional spasms of the eyes of an oculogyric type. The head circumference was 16 in. Eleven weeks after admission she weighed 11 lb. 14 oz. An A.E.G. showed gross evidence of cortical atrophy. Follow-up at 3 years 9 months found the child to be mentally very retarded, weighing 20 lb. 6 oz. and with a head circumference of 18 in.

Case 4. J.V., aged 1 year, because of failure to thrive, was admitted on September 18, 1957, from the Skin Ward where she was under treatment for eczema, hepatosplenomegaly and anaemia. She weighed 9 lb. 14 oz. The head circumference was 14·5 in. She had nystagmus and could not hold up her head. The serum cholesterol, bone marrow and a radiograph of the long bones were all normal. A.E.G. showed evidence of gross cortical atrophy and ventricular dilatation. The child died weighing 8 lb. 2 oz.

Case 5. A.L. was admitted on September 16, 1957, also from the Skin Wards, where she had been found to be suffering from ectodermal dysplasia. The blood urea varied between 56 and 72 mg./100 ml. An intravenous pyelogram showed a normal pattern on the right side and delayed secretion from the left kidney. The child gained 12 oz. in weight in 8 weeks, and at 7 months weighed 8 lb. 12 oz. An A.E.G. showed some ventricular dilatation and gross cortical atrophy.

Case 6. S.J., aged 2 weeks, was admitted on June 10, 1957, weighing 5 lb. 11 oz. Labour and pregnancy had been normal. There was frequent vomiting and at the age of 12 weeks she weighed 5 lb. 15 oz. Subsequent weight gain was slow. An A.E.G. at 5 months showed cortical atrophy as well as some subdural air.

Case 7. V.M., aged 2 weeks, was admitted on December 30, 1957, weighing 3 lb. 3 oz. She had had a minor convulsive episode on the third day of life. The first 8 months of life were spent in hospital during which time she gained weight slowly. She could then hold up her head but could not sit even with support. Both optic discs were pale but she could see and followed objects without making any effort to grasp. A radiograph showed three carpal centres of ossification. An A.E.G. at 8 months showed slight ventricular dilatation and cortical atrophy. A carotid angiogram was done on the right side and showed a normal anatomy of the cerebral vessels. The child died when 16 months of age, weighing 10 lb.

Interpretation of Air Encephalograms

Smith and Crothers (1950) have emphasized the need to interpret, with reserve, air shadows lying over the brain cortex. The common error is to diagnose cortical atrophy because air has entered the subdural space. Subdural air can be recognized by the following features: (1) It moves with alteration of posture of the head. (2) It dips down beside the falx and along the tentorium cerebelli (see Fig. 1). (3) It is smoothly lined and is associated with fluid levels (Fig. 2).

Cortical atrophy can be recognized in the following way: (1) The frontal and parietal regions are predominantly affected (Fig. 3). (2) It produces an irregular picture of peaks and valleys the dilated sulci being usually more than 3 mm. wide (Figs. 4 and 5). (3) If the picture is associated with ventricular dilatation it is diagnostic, but it must be stressed that considerable atrophy of the cortex can occur and yet the ventricles may appear to be normal in size.

Judged by these criteria, all cases in this series had cortical atrophy. It is recognized, however, that a positive diagnosis of brain atrophy based solely on the A.E.G. appearances is not justified. All the infants were at an age when normally rapid brain growth occurs and the changes seen on A.E.G. might have been in part, if not wholly, due to a primary defect in growth rather than an atrophy. No separation of the two types of defect is possible on the evidence available, and in this paper the term atrophy may in fact be covering both a primary defect in cerebral growth and atrophy due to brain damage.

Three facts seem to confirm the diagnosis of cortical atrophy made from these A.E.G.s. Firstly, in those children who have survived and have been followed up, if it was not obvious at first, there has been subsequent clear evidence of brain damage. Secondly, the A.E.G.s of those children with clinical evidence of brain damage differed in no way from those who showed no clinical evidence of damage to the nervous system at the time of A.E.G. Thirdly, confirmation of cortical atrophy was found at necropsy in two other children who had similar A.E.G. changes, but who are not included in this series as their physical development was normal.

It must be stressed that the presenting symptom in these infants was failure to thrive. In Cases 2, 6 and 7 the possibility of cortical brain damage was not at first suspected. These infants were still very young and it was thought that any slowness of intellectual development could be accounted for

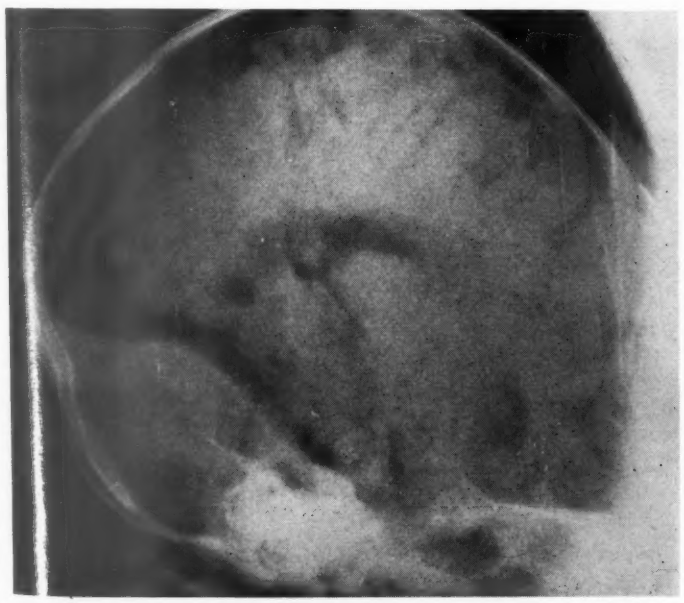

FIG. 1.—Subdural air: showing extension along the tentorium cerebelli.

FIG. 2.

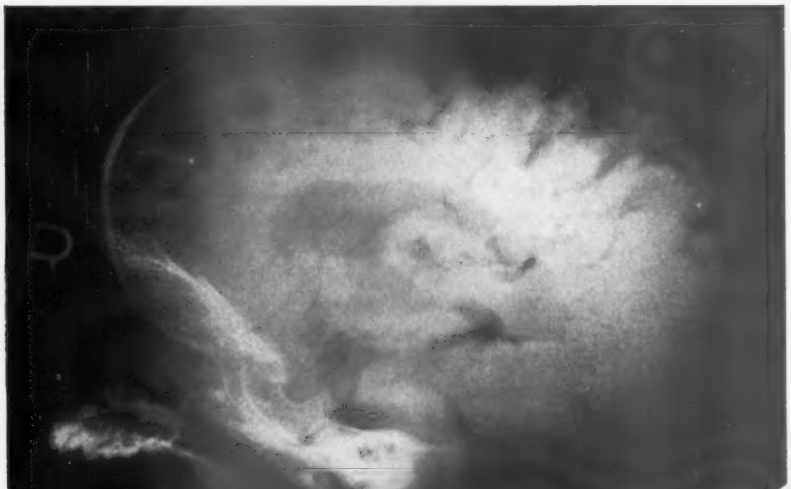

FIG. 3.

FIG. 4.

FIG, 5.

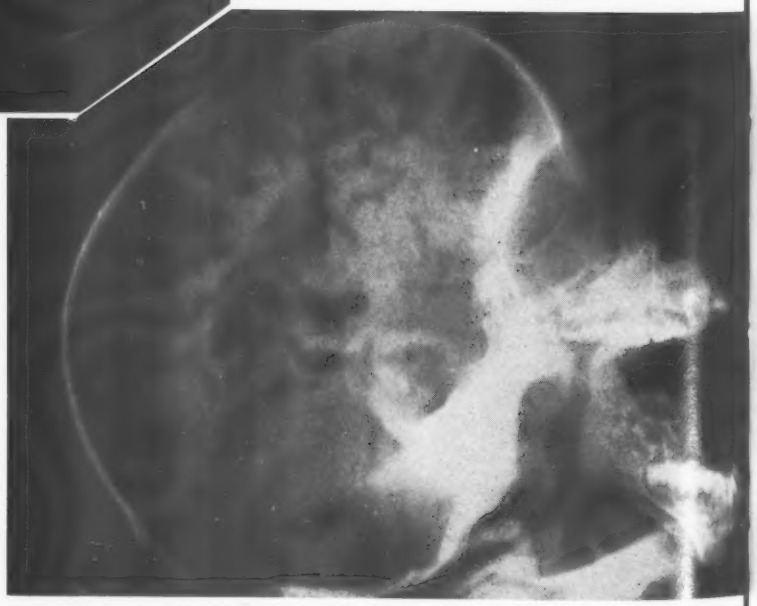

FIG. 2.—Subdural air: showing a fluid level.

FIG. 3.—Cortical atrophy: showing predominantly parietal involvement.

FIG. 4.—Cortical atrophy: A.P. view showing widening of the sulci.

FIG. 5.—Cortical atrophy: lateral view showing widening of sulci.

FIG. 6.

FIG. 7.

FIGS. 6 and 7.—A.E.G.s to show the contrasting picture of dilatation of the ventricular system following pyogenic meningitis.

by the failure of physical growth. Only later, after the infants had been followed for some months, was it realized that the cerebral damage was probably the basic abnormality. Cases 1 and 3 differed from the others only in that they had neurological signs which drew attention to the brain damage. Involvement of areas of the brain that produce definite abnormal physical signs does not, however, seem to be an adequate reason for separating this group from those with no neurological signs. In Cases 4 and 5 there was associated disease that probably contributed to, if it was not the major cause of, the failure to gain weight. Their inclusion seems justified as they showed a similar clinical state and the same changes on their A.E.G.s.

One can only speculate on the cause of the atrophy. There was no familial incidence to suggest a genetic factor. In only one infant was an arteriogram done and this showed no evidence of a vascular defect. It is most unlikely that the cause was a meningitis. Some history of a previous illness should have been obtainable. Furthermore, A.E.G.s done on infants who have had meningitis show an entirely different picture with dilatation of the ventricular system, very little if any air over the cortex and rarely any subdural air (Figs. 6 and 7). In fact the readiness with which the ventricles of children, who have had meningitis, fill, suggests that some other factor plays a part, and that this is possibly dilatation of the whole of the ventricular system including the aqueduct which allows a freer efflux of ventricular fluid and its replacement with air. The atrophy is most likely to be the result of cerebral anoxia, probably intra-uterine or neonatal. Frontal and parietal involvement occurs frequently in such circumstances, and the small size of the heads of these infants also supports the concept of the damage occurring at an early age.

There are many factors governing normal growth and in general growth may be impaired for three main reasons: (1) when diet fails to supply the required nutrients; (2) when there is some breakdown in the physiological process of transporting the nutrients to the tissues; and (3) when the body fails to utilize the nutrients.

Keys (1953) believes that the only neurological causes of failure to thrive are those diseases causing loss of appetite, and those neurological lesions which interfere with feeding. At present no neurological 'centres for growth' are known. Brobeck (1946) states that the hypothalamus normally participates in the maintenance of the overall energy equilibrium

and Brock (1953) ascribes this function to the thalamic hypothalamic level. Lesions of the pituitary might be expected to show delayed ossification of the centres of bone growth. In those children of this series where radiographs of the carpus had been taken, the bone age appeared normal. After damage to the frontal lobes, both clinically and experimentally, a weight loss is frequently observed. Because these subjects frequently manifest voracious appetites, this loss of weight has been ascribed to hypermobility of the intestinal tract (Fulton, Jacobsen and Kennard, 1932). The converse also applies, and a great diminution in appetite, depending on altered prefrontal cortical function, has been described (Brock, 1953). Thus the prime effect of neuronal damage has been an alteration in the hunger drive, with only a secondary nutritional effect. In three of the infants of this series, vomiting apparently of a cerebral type, must have affected growth although it did not always appear either severe or frequent enough to be an entirely satisfactory explanation for the failure to gain weight. In two others there was no vomiting, feeding was normal and appetites were reasonable. When there was some impairment of appetite, tube feeding still failed to achieve a reasonable weight gain. This would suggest that, in some children, cortical atrophy through some subtle mechanism has an adverse effect on the general metabolism resulting in a failure to thrive. The fact that other children with clinical and A.E.G. evidence of cortical atrophy had normal physical development raises the possibility of there being some 'centre for growth' which is affected in some cases and not in others.

In conclusion, it is recognized that the diagnosis of cortical atrophy of the brain is easily made as these infants grow older; but it would be helpful to know the cause of failure to thrive in very young infants when the recognition of mental retardation is not so easy; parents and doctors can then be spared a period of uncertainty as to the nature of the child's illness. In addition unnecessarily prolonged hospitalization can be avoided in those hospitals where there is still a tremendous pressure on beds.

Summary

A series of infants is described in which failure to thrive was the presenting symptom. All of them had heads that were small in circumference and, if not apparent when first seen, subsequently showed evidence of marked mental retardation. All of them had abnormal air encephalograms which were interpreted as indicating cortical atrophy of the brain. In infants the association of cortical atrophy of the brain with failure to thrive does not appear to have been previously recorded.

We wish to thank Professor F. J. Ford for help with the paper; Dr. J. A. Burger, Medical Superintendent of Groote Schuur Hospital, for permission to publish and Mr. Todd for the photographic reproductions.

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THE INCIDENCE OF TWINS IN CEREBRAL PALSY AND MENTAL RETARDATION

BY

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(RECEIVED FOR PUBLICATION OCTOBER 15, 1959)

There is evidence that there is a higher incidence of mental retardation and of cerebral palsy among children born from a multiple pregnancy than among singletons. Asher and Schonell (1950) found that 5·4% of their 400 cases of cerebral palsy were members of twins. Greenspan and Deaver (1953) found that 7% of their 94 cases resulted from multiple pregnancies. The corresponding figure in Shyh-Jong's series of 301 cases (Yue, Shyh-Jong, 1955), was 9·0%.

Looft (1931) found a higher incidence of imbeciles in a group of 64 twins than one finds in the normal population, and among siblings and parents of backward children there were more twins than among normal children. Rosanoff and Inman-Kane (1933) studied 234 pairs of mentally defective twins. They found a higher incidence of mental defects in twins than in singletons. McKinney, Dunphy and Pessin (1958) and Drillien (1959) made similar observations. The latter, in her follow-up of the intelligence quotient of premature babies, found that twins scored less than singletons.

It is not easy to interpret these observations, on account of the higher incidence of cerebral palsy with or without mental retardation, and of mental retardation alone, in prematurely born children, and the high incidence of prematurity in multiple pregnancy.

One could not say, therefore, whether the high incidence of twins in children with mental retardation or with cerebral palsy is merely due to the high incidence of prematurity associated with multiple pregnancy. We therefore set out to elucidate the matter.

An analysis of mentally retarded children or children with cerebral palsy seen at the Children's Hospital, Sheffield did not provide sufficient material for satisfactory statistical conclusions to be made. Accordingly, Dr. Grace Woods of Bristol was asked to cooperate by supplying figures from her large series seen at the Cerebral Palsy Assessment Clinic at the Bristol Children's Hospital (in the case of cerebral palsy), and at a mental deficiency hospital, a mental health clinic and an occupation centre. The Department of Medical Statistics, at the University of Sheffield, analysed the figures.

We made no attempt to distinguish identical from non-identical twins owing to the difficulty of distinguishing these without such accurate methods as the study of blood groups.

The Statistical Problem

The Table sets out the basic data, from which it can be seen that of 729 mentally retarded children, including mongols, 153 (20·9%) were prematurely born, as compared with 234 of 651 children with cerebral palsy (35·9%); of 729 mentally retarded children including mongols, 28 were members of

TABLE
INCIDENCE OF PREMATURITY AND TWINS IN MENTAL RETARDATION AND CEREBRAL PALSY

	Mental Retardation excluding Mongolism or Cerebral Palsy			Mongols			Cerebral Palsy		
	Sheffield	Bristol	Total	Sheffield	Bristol	Total	Sheffield	Bristol	Total
Premature singletons	68	40	108	16	11	27	76	115	191
Full term singletons	274	188	462	46	58	104	155	250	405
Premature twins	8	6	14*	2‡	2	4	12	31	43§
Full term twins	3	6	9†	1	0	1	9	3	12
Total	353	240	593	65	71	136	252	399	651

* Four premature twins were siblings.
† Six full term twins were siblings.
‡ Two premature twins were siblings.
§ Four premature twins were siblings.

twins (3·8%), as compared with 55 of 651 cases of cerebral palsy (8·4%).

Our studies showed that of 375 consecutive premature births in two Sheffield hospitals, 44 children (11·2%) were members of twins (Dr. Ronald Gordon kindly supplied figures for the City General Hospital, Sheffield. The remaining figures were from the Jessop Hospital for Women), and of 252 consecutive twins in the two Sheffield hospitals, 145 (57·7%) were 'premature', weighing 5½lb. (2,500 g.) or less. The incidence of twins in the normal population was taken as 1·2% and the incidence of prematurity as 6·0%.

Results of Statistical Analysis. The high incidence of twins in cerebral palsy is not merely a reflection of the high incidence of prematurity.

The high incidence of twins in mentally retarded children may well be due merely to the high incidence of prematurity.

Discussion

The reason for the high incidence of multiple pregnancy in the history of children with cerebral palsy is unknown. The factors concerned may be partly genetic and partly obstetrical, multiple pregnancies being associated with a high incidence of abnormal presentations and deliveries. The evidence for a genetic factor in some cases of cerebral palsy has been set out elsewhere (Illingworth, 1958).

Summary

We set out to determine whether the high incidence of twins in children with cerebral palsy and with mental retardation without cerebral palsy is merely due to the high incidence of prematurity associated with multiple pregnancy. Statistical analysis has shown that in the case of cerebral palsy the high incidence of twins is not explained by the high incidence of prematurity which is known to be related to cerebral palsy. In the case of mentally retarded children without cerebral palsy the high incidence of twins may well be merely related to the high incidence of prematurity known to be a factor in mental retardation.

Of 729 mentally retarded children without cerebral palsy, 20·9% were prematurely born and the incidence of twins was 3·8%. Of 651 children with cerebral palsy, 35·9% were prematurely born, and 8·4% were twins.

Statistical Addendum

BY

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Estimates of the main probabilities required for a test of significance on the data in Table 1 are given in Table 3. These have been deduced from the facts given in Table 2 using the method of weighted least squares to resolve the inconsistencies of the latter. In doing this, the following points have been borne in mind:

(1) The first two figures of Table 2, though rough,

TABLE 2

INCIDENCE DATA FOR PREMATURITY AND MULTIPLICITY

Incidence of twins in normal population:	1·25%
Incidence of prematurity in normal population:	6%
Incidence of twins among 375 consecutive premature births in two Sheffield hospitals:	11·7% (44 children possibly 22 pairs)
Incidence of prematurity among 252 consecutive twins:	57·6% (145 cases)

TABLE 1

DISTRIBUTION OF CASES ACCORDING TO PREMATURE AND MULTIPLE STATUS FOR DIFFERENT CONDITIONS (BRISTOL AND SHEFFIELD)

		Premature Singletons	Full term Singletons	Premature Twins	Full term Twins	Total
Cerebral palsy	Sheffield	76	155	12	9	252
	Bristol	115	250	31	3	399
	Total	191 (29·3%)	405 (62·2%)	43 (6·6%)	12 (1·8%)	651
Simple mental defectives	Sheffield	68	274	8	3	353
	Bristol	40	188	6	6	240
	Total	108 (18·2%)	462 (77·9%)	14 (2·4%)	9 (1·5%)	593
Mongol idiots	Sheffield	16	46	2	1	65
	Bristol	11	58	2	0	71
	Total	27 (19·9%)	104 (76·5%)	4 (2·9%)	1 (0·7%)	136

have been treated as firm values, i.e. free from statistical error due to paucity of cases.

(2) The standard errors of the other two figures have been assessed from the binomial distribution, taking the birth of a pair of twins as a single random event.

As a preliminary, the mutual compatibility of the Bristol and Sheffield figures in Table 1 was examined by means of χ^2 tests (3 D. of F.) for each of the three conditions. The values were 9·03 (cerebral palsy), 3·23 (simple mental deficiency), 2·24 (mongol idiots); of these the first was significant, on the 5% level only, the other two being not significant. The significance was mainly due to the somewhat smaller percentage of full term twins in the Bristol figures, and was not considered important enough to prevent the two sets of figures being lumped together for further analysis.

TABLE 3

PROBABILITIES OF PREMATURITY AND MULTIPLICITY FROM DATA IN TABLE 2

	Estimated Probability (%)
Premature singleton	5·28
Full-term singleton	93·47
Premature twin	0·72
Full-term twin	0·53
Total	100·00

NOTE.—The second decimal is given to avoid accumulation of rounding off errors in working.

Since the incidence of twins is small, the number falling into any given category can be taken as a Poisson variate, provided that only one of a pair of siblings is included in the count. Also since Poisson variates are additive, results for premature and full term children may be added for the purpose of a test of significance. These two considerations lead to Table 4, the significance of the discrepancies being assessed by reference to the Poisson tables; the expected numbers are deduced by applying the incidence rates of Table 3 to the numbers of premature and full term cases at risk in the various categories. No allowance has been made for statistical errors in the expected numbers arising in their derivation from the data in Table 2, and thus will tend to lead to a slight overstatement of the level of significance; notwithstanding this, the results are clear enough for there to be no doubt of the *significantly greater incidence of twins among cases of cerebral palsy*. On the other hand, there is no evidence of an abnormal incidence of twins in the presence of either of the other conditions.

TABLE 4

OBSERVED AND EXPECTED INCIDENCE OF TWINS FOR DIFFERENT CONDITIONS

	Observed Number		Expected Number		Significance of Discrepancy
Cerebral palsy	54		30·3		0·1% level
Simple mental defectives	20	24	17·2	21·4	Not significant even on 5% level
Mongol idiots	4		4·2		

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CONVULSIVE MOVEMENTS OCCURRING IN THE FIRST 10 DAYS OF LIFE*

BY

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(RECEIVED FOR PUBLICATION OCTOBER 7, 1959)

It has been estimated that approximately 6% of children under the age of 5 years have convulsions due to one cause or another. Moreover, it is generally recognized that this liability to convulsive incidents is greatest in infancy. There is little mention in the literature of the extent to which these generalizations apply to the early days of life, although it is well known that convulsions in newly-born infants occur in a wide variety of circumstances. I present here the results of a study of convulsions occurring for the first time within 10 days of birth.

The Clinical Material

Three hundred and seventy-five babies are included in the study, of whom 158 died and came to autopsy, and 216 survived the neonatal period. With a few exceptions the infants were born in the Simpson Memorial Hospital, Edinburgh, or the Maternity Hospital, Leeds. The exceptions had been delivered elsewhere and subsequently transferred to one or other of the above-mentioned hospitals. All 374 babies were seen personally and were under continuous clinical supervision for a period of not less than 10 days unless death intervened.

Fatal Cases (158): Pathological Findings

The pathological findings in the 158 fatal cases are analysed in Tables 1 to 5. Significant non-infectious intracranial pathological changes were present in almost two thirds of the babies. Infection, developmental anomalies and haemorrhage (other than intracranial) were present in that order of frequency in the remaining fatal cases. Findings were completely negative at nine autopsies (Table 1).

There was evidence of intracranial infection (Table 2) in 18 and of septicaemia without intracranial involvement in seven babies. Infection was coliform in nine, streptococcal (haemolytic) in two, pneumococcal in one and staphylococcal in two of the 14 babies with septicaemia and meningitis. Blood obtained during life from the seven infants with septicaemia without meningitis gave cultures of *Esch. coli* in four, *Staphylococcus aureus* in two, and streptococcus in one. The strain of streptococcus was not established. Of the four cases of otitis media three were the result of pneumococcal and one of staphylococcal infection. Pyelonephritis was associated with coliform infection in two babies and with *Staphylococcus aureus* infection in one. The primary focus in babies with staphylococcal infection was in the eye in one, the ears in one and the skin in four cases, the majority of which occurred before the advent of antibiotic therapy. Neither brain nor meninges was the site of pathological changes in the babies with pyelonephritis and congenital syphilis.

With regard to deaths contributed to by developmental anomalies (Table 3) the three examples of

TABLE 1

CONVULSIONS IN THE FIRST 10 DAYS OF LIFE
FATAL CASES: MAJOR AUTOPSY FINDINGS

Infection	29
Developmental anomalies	14
Acquired (non-infectious) intracranial pathology	97
Haemorrhage other than intracranial	9
Nil	9
	158

TABLE 2

CONVULSIONS IN THE FIRST 10 DAYS OF LIFE
FATAL CASES: DEATHS DUE TO INFECTION

Septicaemia with meningitis	14
Septicaemia	7
Otitis media with secondary meningitis	3
Pyelonephritis	3
Otitis media with secondary brain abscess	1
Congenital syphilis	1
	29

* Based on lectures given at the University of Bergen and to the Medisinsk Selskap, Oslo.

internal hydrocephalus all occurred in small premature infants. The renal and cardiovascular abnormalities were of a major character and incompatible with survival. Infants with evidence of cerebral agenesis are referred to later.

TABLE 3

CONVULSIONS IN THE FIRST 10 DAYS OF LIFE
FATAL CASES: DEATHS CONTRIBUTED TO BY DEVELOPMENTAL ANOMALIES

Cerebral agenesis	6
Internal hydrocephalus	3
Cardiac with associated transposition of great vessels	2
Hydronephrosis (with secondary infection)	2
Cystic kidneys	1
	14

Haemorrhage contributed to death in a variety of ways (Table 4). Massive intrapulmonary haemorrhage was a feature in two cases, in one of which there was microscopical evidence of early secondary staphylococcal infection. Of the two examples of fatal exsanguination one was the result of incision of the placenta in the course of delivery by caesarean section and the other of massive intestinal haemorrhage in a baby with untreated haemorrhagic disease who had been born outside hospital. All the examples of suprarenal haemorrhage were massive and associated with widely distributed tardieu spots. In none of the cases was there a history of trauma or evidence of infection and I cannot say whether the suprarenal haemorrhages were the cause or the result of associated asphyxia. Suprarenal haemorrhage certainly was the immediate cause of death in each case.

TABLE 4

CONVULSIONS IN THE FIRST 10 DAYS OF LIFE
FATAL CASES: DEATHS CONTRIBUTED TO BY HAEMORRHAGE OR CONGESTION

Intrapulmonary haemorrhage	2
Exsanguination	2
Suprarenal haemorrhage	5
Intracranial haemorrhage, venous congestion or oedema	97
	106

Haemorrhage within the cranium was found in a number of different situations (Table 5). In many instances post mortem findings pointed to asphyxia having been secondary to traumatic haemorrhage. In an equal number it was not possible to differentiate the relative aetiological significance of coexistent haemorrhage and asphyxia. This was especially true of a high proportion of infants with subarachnoid and intraventricular haemorrhage. In two infants intracranial haemorrhage was associated with bleeding into the peritoneal, pleural and pericardial sacs which was regarded as evidence of haemorrhagic disease; and in one baby bleeding arose from septic thrombosis of the choroid plexus in the presence of staphylococcal septicaemia without meningitis. Aseptic thrombosis of the choroid plexus with secondary intraventricular haemorrhage was found in six babies all of whom were markedly premature and died after the tenth day of life. In two of these babies there was, in addition, thrombosis of the renal vessels and in one, dry gangrene of the toes secondary to thrombosis.

Severe generalized venous congestion or extensive oedema was the only finding in about 15% of the fatal cases with acquired non-infectious intracranial pathology.

Pneumonia was present in 13 of the infants coming to autopsy, but was considered to be a terminal complication in each instance.

TABLE 5

CONVULSIONS IN THE FIRST 10 DAYS OF LIFE
FATAL CASES: ACQUIRED (NON INFECTIOUS) INTRACRANIAL CONDITIONS

Haemorrhage:	subdural	30
	subarachnoid	14
	intraventricular	23
	multiple perivascular in brain substance	6
Venous congestion involving meninges and brain substance		9
Generalized oedema		7
Sinus thrombosis		4
Kernikterus		4
		97

Surviving Cases (216): Diagnoses

Surviving cases are best considered according as the clinical diagnosis was proven, being confirmed by appropriate laboratory studies, or was conjectural, being based upon clinical observations.

Proven Diagnoses. Table 6 lists the 38 cases in which a firm diagnosis was made. Infection was present in 15. Pyelographic investigations were not considered desirable or practicable in the cases of urinary infection. The possibility of renal abnormalities in these cases was not therefore excluded, but none of the infants concerned had a recurrence of signs or symptoms by the age of 2 years. Exsanguination resulted in one infant from prolonged, severe intestinal bleeding due to haemorrhagic disease, and in the other infant was thought after examination of the mother's blood to be due to foetal intraplacental haemorrhage. Both infants were born at home and there was delay in diagnosis and treatment. The patients with cerebral agenesis are described later. Convulsions started on the tenth day of life in each of the babies with subdural effusions. The fontanelle

TABLE 6

CONVULSIONS IN THE FIRST 10 DAYS OF LIFE SURVIVING BABIES: PROVEN DIAGNOSES (38)

Diagnosis	Confirmation	No. of Cases
Meningitis: *Esch. coli*	Bacteriological	3
Pneumococcus	Bacteriological	2
Meningococcus	Bacteriological	1
B. friedlanderi	Bacteriological	1
Proteus	Bacteriological	1
Pyelonephritis	Cytological: Bacteriological	7
Exsanguination	Clinical, haematological and therapeutic	2
Cerebral agenesis	Air encephalography	11
Subdural effusion	Aspiration: Air encephalography	2
Kernikterus	Serological and biochemical	6
Tetany	Biochemical	2

was a little tense and the resistance on percussion of the two sides of the cranium differed. A tentative diagnosis leading to confirmatory aspiration was not made until some weeks later by which time convulsions were recurring at intervals of several days. In the two infants with tetany, convulsions occurred as the culmination of particularly exhausting periods of severe generalized neuromuscular hyperexcitability and coincided with depression of the serum calcium level below 6 mg./100 ml. Both babies were the offspring of mothers with diabetes mellitus (Craig, 1958).

Presumptive Diagnoses. The presumptive diagnoses in 178 surviving infants are given in Table 7. In over 80% of these babies the diagnosis was intracranial disturbance. This term is used deliberately as it is only rarely possible to differentiate clinical signs of intracranial disturbance during life due to cerebral haemorrhage, congestion and oedema. It might be argued that lumbar puncture would have assisted in differential diagnosis. In my opinion this is open to question and lumbar puncture should be reserved for those cases in which the need arises to exclude meningitis. Potter (1952) draws attention to the limited value of examination of the cerebrospinal fluid as a diagnostic measure in cerebral haemorrhage.

With regard to other cases included in Table 7 the diagnosis of poliomyelitis in a baby in whom two isolated convulsions occurred on the tenth day of life was based on a history of contact, a temporary pronounced increase of lymphocytes in the cerebrospinal fluid and a residual flaccid paresis and muscle wasting still present in the left lower limb at the age of 4 years. No convincing explanation of the case labelled '?-aseptic meningoencephalitis' can be offered. There was no clue in the birth history. The child was born at term. Progress was uneventful apart from a succession of violent general convulsions on the eighth day of life and the presence of nuchal rigidity for several days. Cells in the cerebrospinal fluid were greatly increased for a week, lymphocytes predominating, but successive bacteriological cultures were consistently negative. At 3 years of age the child's condition was in every way normal.

TABLE 7

CONVULSIONS IN THE FIRST 10 DAYS OF LIFE SURVIVING BABIES: PRESUMPTIVE DIAGNOSIS (178)

Poliomyelitis	1
?-Aseptic meningoencephalitis	1
Alimentary disturbance (non-infectious)	7
Aspiration of feeds	4
Hypothermia	9
Cold injury	4
Intracranial disturbance	152
	178

Five of the seven cases listed as alimentary disturbance were similar. A violent convulsion in the second week of life in a previously healthy baby occurred simultaneously with the passage of an abnormally bulky stool containing numerous large undigested curds. The association between convulsion and manifestly abnormal stools was inescapable. Convulsion and stool were completely isolated incidents. There was neither forewarning nor aftermath. The other two infants in this group were very small premature babies in whom the initial expulsion of meconium was delayed until the sixth day of life due, it was considered, to lack of muscle tone. There was no question of meconium ileus or mucoviscidosis. Generalized twitching movements appeared on the sixth day and did not recur after the removal of the retained meconium by gentle low colonic lavage. Asphyxial convulsions due to aspiration of feeds were due to a lapse in nursing technique in the case of one infant; to difficulty in feeding another baby with a suspected but at the time undemonstrated high, short tracheo-oesophageal fistula; and to injudiciously repeated feeds given to two infants with undiagnosed oesophageal atresia.

Use of the term hypothermia in Table 7 implies that a rectal temperature below 95° F. persisted for a period of not less than 24 hours. Hypothermia was a feature also of the four babies with cold injury, being associated with the hard infiltration of skin, subcutaneous tissues and muscles found in this condition which is variously, confusingly and frequently incorrectly referred to in the literature as sclerema, scleredema, scleroderma and cold injury (Macgregor, 1960). For the purposes of this paper the term cold injury is employed throughout.

Details Concerning Convulsions

The clinical characteristics of convulsions seen in the course of the present study varied considerably. Examples were seen of a tonic phase followed in succession by clonic movements and unconsciousness; of isolated, prolonged tonic incidents; and of both brief and persistent clonic phases not preceded by tonicity or followed by unconsciousness. In some instances the onset of a convulsion was immediately preceded by or coincided with a short and sometimes piercing cry; in others grunting or crying was noted during or at the termination of a phase of tonicity. A cry was absent in most cases. Violent generalized convulsions were seen with noteworthy rarity in premature babies. Rhythmic clonic movements were common; involved one or several limbs at any one time; frequently affected different limbs at different times: and were often associated with transient unilateral twitching of muscles at the angles of the mouth or eyes. Associated cyanosis, neck rigidity and opisthotonus were occasional findings.

Convulsions Considered in Relation to Diagnosis.

INFECTIONS. Convulsions in babies with septicaemia or meningitis consisted of fitful phases of subdued clonic movements with irregularly interspersed brief events of apnoea. In some infants these incidents occurred spontaneously and in others only when disturbed. Convulsive movements did not appear until after the third day of life even in infants in whom the obstetrical history suggested that infection had been antenatal. The fact that all the infants concerned were premature and frail probably accounted for the convulsions not being severe. In fatal cases there was no relationship between the clinical picture and the location, the extent or the bacteriological nature of the infective process as seen at autopsy. A feature of white blood cell counts during life was that a severe leucopenia was as common as a pronounced leucocytosis. Convulsions occurring in infants with pyuria were generalized but not severe in character, and commenced before the onset of the swinging temperature characteristic of the condition. They ceased as diuresis increased.

DEVELOPMENTAL ANOMALIES. Convulsions seen in babies with major anomalies of the cardiovascular system and of the kidneys were violent terminal events. The infants with internal hydrocephalus were premature and small, and the convulsions consisted of sporadic twitching movements. In marked contrast, babies with cerebral agenesis presented clinical pictures remarkable for their severity and similarity of pattern. The convulsions first appeared about the second day of life, thereafter occurring spontaneously at frequent but wholly irregular intervals, and persisted despite large and frequent doses of chloral hydrate and phenobarbitone. Structural asymmetry or unusual configuration of the face or cranium was a feature in a significant number of these infants.

HAEMORRHAGE. The convulsions which took place in the presence of external bleeding were isolated but severe and general in distribution. Those that occurred in fatal cases were terminal events. In the two babies who survived exsanguination the convulsions were similar in character and occurred when the infants arrived at hospital *in extremis*, having been transported without previous treatment over distances exceeding 40 miles. Copious haemoptysis preceded the terminal convulsions in babies with massive intrapulmonary haemorrhage. Convulsions in infants with massive suprarenal haemorrhage at autopsy began suddenly a few hours before death and assumed a violent form even when the baby was small and premature. They were accompanied by collapse and tachycardia and in two cases by sweating of abnormal degree.

INTRACRANIAL DISTURBANCE. Convulsions in babies developing kernikterus were subdued in character, recurred at intervals of widely varying length over a period of days and showed great variability in the parts of the body involved. Cycling movements of the lower limbs and boxing movements of the arms were among other features in these infants. The convulsions in the infants with subdural effusions began in the middle of the second week, were vigorous and general and associated with occasional vomiting. Personal experience suggests that the cases were exceptional in that vomiting attributable to subdural effusion usually precedes convulsions which more commonly first appear after the second week of life.

Consideration of intracranial disturbances presents special difficulties. Among babies with subdural haemorrhage major generalized convulsions were a feature in about 50%. Regardless of their severity and whether they were generalized or localized, convulsions tended to recur over a period of 24-36 hours. They contrasted with convulsive movements associated with other forms of intracranial haemorrhage in the readiness with which they were induced by external stimuli. Progressively deepening cyanosis during life was usually accounted for by pressure exerted on the mid brain by large amounts of blood which had gravitated downwards. There was no constant association between generalized convulsions and the distribution of blood over the cortex. Localized convulsive

movements were seldom explained by the anatomical distribution of bleeding.

Clinical features in babies with subarachnoid haemorrhage lacked the drama of those in cases of subdural haemorrhage. Localized slight convulsive or twitching movements were present in about half the infants with subarachnoid haemorrhage. Generalized convulsions were rare. There was no significant correlation between the extent of the subarachnoid haemorrhage and the severity or localization of the convulsive movements. An unexplained finding was the frequency with which twitching was preceded by abnormal movements of the eyes. Intraventricular haemorrhage is sometimes found unexpectedly at autopsy without any signs of cerebral irritation during life. When they did occur convulsions were dramatically sudden in onset, of extreme violence and accompanied by uncoordinated movements of the eyes and piercing cries of intense cerebral pain. These signs were present in 10 babies, of whom seven died in the first, and three in the second week. In five babies isolated slight twitchings were noted for a few hours before the development of major convulsions. The clinical pictures in the six babies with widely distributed intracranial perivascular haemorrhages were strikingly similar. In all the appearance of convulsions was delayed until the second week. From the time of their onset the convulsions were general, of extreme violence and completely exhausting. Persistent restlessness was characteristic. Death occurred suddenly after a period of wild uncontrollability similar to that sometimes seen in small babies with fulminating encephalitis. I have known only two babies survive after presenting this clinical picture. Both were eventually severely handicapped, physically and mentally, and both were ultimately ataxic.

During life the clinical pictures presented by infants with severe intracranial oedema at autopsy were indistinguishable from those due to other forms of intracranial disturbance.

HYPOTHERMIA AND COLD INJURY. Convulsions in babies with hypothermia were general but not violent, and although not frequent, occurred at lengthy irregular intervals until the body temperature was raised. Similar findings were encountered in the two babies with cold injury, but it was evident that as the stiffness or rigidity characteristic of the condition increased, fine frequent convulsive movements became more coarse and deliberate.

The Incidence of Convulsive Movements

In one hospital to which admissions are subject to obstetrical selection, and at which detailed clinical notes have been kept over many years, the records suggest that one infant in approximately every 120-125 live births has convulsive movements at some time during the first 10 days of life. The incidence is certainly considerably less, although exact figures are not available, in another hospital, with which I am associated, which is of about the same size and which admits only multiparous and uncomplicated maternity cases.

The incidence of convulsions in relation to certain clinical conditions seen in newly-born babies was also studied. Table 8 summarizes the findings.

The Severity of Convulsive Movements and Long Term Prognosis

A follow-up study was made of 141 of the 152 infants who survived the neonatal period and who

TABLE 8

INCIDENCE OF CONVULSIONS OCCURRING IN THE FIRST 10 DAYS OF LIFE IN ASSOCIATION WITH CERTAIN CLINICAL CONDITIONS

Clinico-Pathological Group	Number of Infants						% of Infants with Convulsions
	Dying†		Surviving†		Total		
	Convulsions		Convulsions		Convulsions		
	With	None	With	None	With	None	
Cerebral agenesis	6	2	11*	2	17	4	81
Septicaemia and/or meningitis	24	10	8	2	32	12	73
Intracranial disturbance	97	‡	152	488	249	‡	Less than 33
Renal anomalies	3	11	—	—	3	11	—
Kernikterus	4	6	6	4	10	10	50
Severe urinary infection	3	3	7	58	10	61	14
Cold injury	—	3	4	15	4	18	18
Haemorrhagic disease	1	1	2	149	3	150	2
Hypocalcaemic tetany	—	—	2	63	2	63	3
Suprarenal haemorrhage	5	10	—	—	5	10	—
Internal hydrocephalus	3	6	—	—	3	6	—
Intrapulmonary haemorrhage	2	8	—	—	2	8	—

* Six of these infants died in the second year of life. † Relates to first four weeks of life. ‡ Reliable figures not available.

in the first few days of life had shown convulsive tendencies attributed at the time to intracranial disturbance. Of the 141 babies nine died before the age of 2 years and the remaining 132 were last examined between the ages of 3 and 3½ years. Findings were analysed according as the postnatal convulsions had been violent and general, or transient and slight; and were compared with those in a control series consisting of 488 babies who had had no convulsions but had shown signs of postnatal anoxia and distress, and who were re-examined at or shortly after the age of 3 years (Table 9). The figures do not purport to be statistically accurate but reflect a higher incidence of sequelae in babies with a history of neonatal convulsions than in babies with no such history.

TABLE 9

NEONATAL ASPHYXIA/INTRACRANIAL DISTURBANCE WITH AND WITHOUT CONVULSIONS: SURVIVING BABIES; FINDINGS AT OR OVER THREE YEARS OF AGE

Findings at 3 Years of Age or Over	Neonatal Convulsions Number of Babies					
	None		Prolonged/ Severe		Transient/ Slight	
Normal	473		85		45	
Physical handicap	6		1		—	
*Mental handicap	3	3%	1	7·5%	1	8%
*Physical and mental handicap	6		5		3	
Total	488		92†		49‡	

* Does not include children considered to be primary aments.
† Includes 9 babies of birth weight of 5½ lb. or less.
‡ Includes 31 babies of birth weight of 5½ lb. or less.

Discussion

The evidence presented indicates that whereas it has been variously stated that 2-4% of children under 3 years (Green and Richmond, 1954) and approximately 6% under 5 years (Davidson, 1953) have convulsions, considerably less than 1% of babies in maternity hospitals have convulsions within 10 days of birth. This is of interest in view of the greater liability to convulsions of infants as compared with older children (Davidson, 1953) and of the findings of Crump (1945) which show that the incidence of convulsions is lowest in the first six months of life and highest between the ages of 6 months and 3 years.

Asphyxia, cerebral birth injury, meningitis, systemic infections, kernikterus, congenital malformations and metabolic disturbances such as tetany are among causes of neonatal convulsions given in the majority of reviews. In a study of 176 babies aged less than 4 weeks, Peterman (1946) considered that convulsions were accounted for by birth injury in 69%, acute infection in 10%, developmental anomalies in 4% and tetany in 3%. The present series includes examples of all these conditions together with instances of convulsions associated with exsanguination, intrapulmonary haemorrhage and cold injury. Clifford (1939), Ford (1952), Stone (1945) and McQuarrie and Baird (1959) consider that haemorrhagic disease contributes to a proportion of cases of intracranial haemorrhage. Findings in this study confirm the views of other workers that this is not a frequent occurrence (Craig, 1938; Potter, 1945; Sanford, Shmigelsky and Chapin, 1942). Kagan (1959) makes specific mention of gastro-enteritis. This is contrary to my experience. In a detailed review of 53 cases of acute enteritis in the newly-born in both epidemic and sporadic form no instance of convulsions was encountered.

Recent literature does not refer to alimentary disturbances other than gastro-enteritis as a cause of convulsions in infancy. Thomson (1921), Still (1927) and Hutchison (1931), however, all mention the occurrence of convulsions as a result of the retention of undigested food in the bowel or stomach. They ascribe the convulsions to reflex irritation. Today this explanation is considered inadequate. Nevertheless, in the absence of a convincing alternative and in the absence of evidence of metabolic disturbance the explanation merits consideration in connexion with the few babies in the present series in whom isolated convulsions coincided with the evacuation of undigested stools.

Febrile convulsions are described by Green and Richmond (1954) and McQuarrie and Baird (1959) as especially common in the first two years of life. Davidson (1953) stressing their occurrence in infants considers that of convulsions in all children 2·5% are regarded as 'so-called febrile convulsions'. According to Friderichsen and Melchior (1954) febrile convulsions are rarely seen under the age of 6 months. The youngest patient in 256 children with simple febrile convulsions reported by Livingston (1958) was aged 2 months. Discussing febrile convulsions in general, McQuarrie and Baird (1959) refer to the onset of extracranial infections and to a high environmental temperature as possible contributory factors. An outstanding feature of the series under discussion is the absence of any baby with convulsions which could reasonably be termed febrile in the strict sense of the term. In the few babies with severe urinary infection in whom convulsions occurred the temperatures were subject to fluctuation and were elevated on occasions to 102°-103° F. Pyrexia of the same degree was a feature of the considerably more numerous cases of pyuria lacking any convulsive tendency. Among

infants with meningitis and septicaemia a normal or slightly subnormal temperature was as frequent a finding as an elevated temperature. Pyrexia when present was usually slight. There was no obvious connexion between body temperature and the occurrence of convulsions in these cases. Experience gained in the course of the present study warrants the view that febrile convulsions if they do take place in the first 10 days of life do so with the utmost rarity. There is support for this opinion in the fact that dehydration fever is not accompanied by convulsions. Moreover, over a period of many years I have seen and made records of five newly-born babies with extreme hyperpyrexia attributable to faulty nursing technique or defective incubator control. The rectal temperature ranged from 106° to 108° F. and in each case hyperpyrexia was present for not less than six hours. All the babies recovered without sequelae. None had convulsions. Unfortunately records were not made concerning the rapidity with which the temperatures rose, an aspect of febrile convulsions considered to be important by Wegman (1939).

Severe, extensive cerebral oedema was the sole finding at autopsy in five cases. It was also found in less severe degree in association with other forms of intracranial pathology in three babies born prematurely and in two born at term. The clinical simulation of intracranial haemorrhage by babies with cerebral oedema is noted by Hughes (1952), and McQuarrie and Baird (1959) include acute cerebral oedema among the causes of convulsions in infancy. Judging by the incidence of cerebral oedema among fatal cases in the present series it is possible, indeed probable, that cerebral oedema may account for a considerable number of convulsions in surviving newly-born babies. Certainly cerebral oedema provides one possible explanation for the convulsions occurring in two of the surviving examples of cold injury.

Hypothermia is characteristic of cold injury and was a feature of the two cases in this series. It was a feature also of several of the premature babies dying of infection, and of several infants dying as a result of intracranial haemorrhage. Furthermore, among large babies surviving neonatal cerebral disturbance, convulsions occurred in a number within 36 hours of birth while the body temperature was still below 96° F. There were several examples of twitching movements occurring simultaneously with a sudden drop in body temperature on the third and fourth days of life in particularly small premature babies who eventually survived. These observations do not warrant any conclusions but suggest that a closer relationship may exist between convulsions in the first few days of life and hypothermia than between convulsions and hyperpyrexia.

Bound, Butler and Spector (1956) in their study of perinatal mortality refer to the occurrence of convulsions in 20, and of cerebral irritation without convulsions in six premature babies dying as a result of the cardio-respiratory syndrome. Their experience contrasts with that at the Leeds Maternity Hospital where over a number of years continuous detailed clinical observations have been made on all infants in whom there was a possibility that signs of the cardio-respiratory syndrome might develop.

During the period in question 38 babies dying with clinical and pathological evidence of the syndrome were observed from the time of delivery in the labour ward until death, with as one particular object the recognition of any convulsive tendencies. All the babies were premature and delivered by caesarean section. Entirely contrary to expectations no convulsions were seen in any of the infants. Insofar as a limited number of cases permits of tentative deductions it seems that the anoxia occurring in fatal cases of the cardio-respiratory syndrome does not of itself give rise to convulsions. A further point is that these cases are not associated with the generalized tonicity and apnoea sometimes seen in very small premature babies. It is of interest in this connexion that McKay and Smith (1959) do not include convulsions among the clinical manifestations of hyaline disease.

'The causes of convulsions (in infants) are legion.' This statement of Still's (1927) can be applied with justification to the newly born. It is important, however, that the occurrence of convulsions in the early days of life should be seen in proper perspective. Although the causes are legion the analysis in Table 8 indicates that no one clinico-pathological condition is invariably associated with convulsions. The highest incidence was found in babies with cerebral agenesis. Of the 21 babies, no fewer than 17 had major convulsions. The clinical pattern in these was unlike that associated with other forms of intracranial pathology, and it is considered that it has a diagnostic significance. Particular attention should be paid in this connexion to major convulsions commencing within a day or two of life, persisting at irregular intervals despite heavy anticonvulsant therapy, and occurring in an infant with asymmetrical anomalies of the face or cranium.

There was a high incidence of convulsions among babies with septicaemia and meningitis. Convulsions cannot, however, be regarded as fundamental to diagnosis. They were absent in a number of babies with widely dispersed septicaemic foci and

thick inflammatory exudate covering the entire surface of the brain. Clinical features requiring the exclusion of infection as a cause of convulsions include the presence simultaneously of an unexplained low body temperature, grey cyanosis and reluctance to feed. A leucocytosis or leucopenia is in favour of infection whereas a normal white cell count is not.

This study makes it abundantly clear how rarely a precise diagnosis is possible during life. Convulsions in the presence of unconsciousness and of deepening cyanosis not responding to oxygen therapy suggest pressure on the mid-brain or brain stem by haemorrhage arising from a dural tear. An uncontrollable encephalopathic picture punctuated by convulsive seizures following difficult delivery of a large or post-mature infant is suggestive of intracerebral and/or intracerebellar multiple perivascular haemorrhages. The dramatically sudden appearance in a premature baby of violent, generalized convulsions, a bulging fontanelle and an agonizingly piercing cry is in keeping with intraventricular haemorrhage. Otherwise there is no clinical picture (apart from that already described in connexion with cerebral agenesis) characteristic of intracranial pathology of a particular kind or with a particular anatomical location.

Terminal convulsions irrespective of their pathological explanation and of the maturity of the infant tend to be violent and general. In other circumstances convulsions encountered in small premature babies are generally of a subdued character. Mention has been made of the occasional simultaneous occurrence in these babies of transient cyanotic apnoea and generalized tonicity. Incidents of this kind can occur as completely isolated events or as events interspersed between phases of subdued twitching or myoclonic activity. As Green and Richmond (1954) point out, young infants may demonstrate only the tonic phase of a major convulsion. There were occasions when even momentary apnoeic attacks might in reality have been minimal convulsive incidents, but they were not regarded as such for the purposes of this study. Nevertheless, the extent to which the frailty of prematurity tends to subdue the severe manifestations of convulsive tendencies was very evident. For this reason it is considered that assessment of the potential risks of convulsions in the early days of life must have regard to the maturity and physical robustness or otherwise of the baby.

Observations made in the present study do not agree with the conclusion of Keith, Norval and Hunt (1953) that 'difficulties during delivery have very little to do with persistent neurological abnormalities' in surviving infants, and do not support the view advanced by Hellström and Jonsson (1953) that asphyxial attacks appearing 'later on and after the child has breathed normally' have a less favourable prognosis. The findings in the follow-up series (Table 9) do suggest, however, that the general risk of morbid sequelae is as great in the case of premature babies with slight transient convulsions as in babies born at term having prolonged major convulsions.

Summary

The clinical findings in 374 newly-born babies who had convulsions commencing within 10 days of birth are presented.

The pathological findings in 158 fatal cases are considered in relation to clinical observations made during life.

Surviving cases are considered according as the diagnoses were proven or presumptive.

Attention is drawn to the characteristics of convulsions arising in cases of cerebral agenesis.

Emphasis is attached to the absence of 'febrile convulsions' and of convulsions in association with uncomplicated cardio-respiratory syndrome.

The occasional occurrence of convulsions in the presence of cerebral oedema and hypothermia is noted.

The influence of prematurity and the prognostic significance of transient minimal convulsions in premature babies are discussed.

The study was only made possible by the courtesy of senior obstetrical colleagues and by the enthusiastic assistance of a succession of registrar colleagues too numerous for individual mention. I am indebted for assistance to Miss M. Pattullo and Sister R. White in making clinical observations, and to the Librarian, the Royal College of Physicians, Edinburgh, in obtaining references. Especial thanks are due to Dr. Agnes Macgregor, Dr. W. Goldie and Dr. D. G. F. Harriman for their invaluable criticism and advice.

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FAMILIAL DIFFUSE PROGRESSIVE ENCEPHALOPATHY

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(RECEIVED FOR PUBLICATION OCTOBER 21, 1959)

The purpose of this paper is to present the clinical and neuropathological findings in two idiot brothers in whom the mode and time of onset and the pattern of brain anomalies were remarkably similar. Clinically there were similarities with well-known syndromes such as Tay Sachs and Schilder's disease. However, the ultimate diagnosis was to emphasize the frequent difficulties encountered in determining the aetiology of mental deficiency with progressive neurological features.

Family History

The parents, each an only child, were English and in good health. There was no history of consanguinity, mental illness, epilepsy, ataxia, blindness, skeletal deformity or other neurological disease in three generations of the family.

Case Histories

Case 1. This child, the first, was born when the father was 29 years old and the mother 28. The mother attended an antenatal clinic and, after seven months gestation, developed hydramnios. Pregnancy was otherwise normal as far as is known and the baby was born at full term. The presentation was occipito-posterior, labour was prolonged, and the child was delivered by forceps. No asphyxia was noted at birth but the child's head was bruised. The birth weight was 9 lb. 3 oz. (4,160 g.). He was regarded as normal until 3 weeks old, when epileptiform movements were noticed on several occasions. At 6 weeks these movements started again. They consisted of a spasmodic twitching of the neck to the right, and of the left arm and leg, and increased in severity to involve the whole body, which became straight and rigid with the head and eyes deviated to the left and the face becoming red. To begin with he had between two and four such attacks a day but this became increasingly more frequent until he was having between seven and 10 or more, despite treatment with phenobarbitone.

Initially, he was breast fed but at 7 weeks increasing difficulty with sucking made it necessary to substitute spoon feeding. Up to this time he had been considered a normal child mentally and physically, apart from the seizures. From then on he deteriorated and at the age of 3 months he was described as lying helpless and barely able to move his limbs. He never smiled and appeared to be blind. By the age of 3 years and 2 months he was described as inert, silent, helpless and drowsy all day. He was unable to sit up and could move only his right leg slightly. He failed to respond to any stimuli except painful ones which provoked a monotonous scream. He was deaf and speech had not developed. Feeding was difficult because of the extreme slowness in swallowing. He suffered from severe constipation. Mentation and behaviour were such that both were described as 'less than that of a new born child'. He had no grasp reflex and his developmental quotient was zero.

CLINICAL FINDINGS. On admission to the Fountain Hospital he weighed 10·6 kg., height 84·2 cm. (normal for age and sex is 14·61 kg., height 96·7 cm.).

At 3 months old his head was markedly asymmetrical, though its circumference (45·1 cm.) was slightly larger for age (normal: 40·9 cm.). At 3 years 2 months the circumference (49·5 cm.) was still within normal limits (normal: 50·4 cm.), but the asymmetry was more marked. The left frontal region had become very prominent and there was left occipital bossing. His teeth were yellowish. A spastic paralysis was more marked on the left side, especially the leg. There was a right facial weakness, the right palpebral fissure being wider than the left and the movements of the muscles of the forehead and the right side of the mouth being diminished. Contractures of the wrist flexors were present, the hand being flexed at the metacarpophalangeal and extended at the interphalangeal joints. A severe thoracolumbar scoliosis and talipes equino-varus was observed. Babinski's sign was positive on both sides and the knee and other tendon jerks were exaggerated while the abdominal reflexes were absent. A light bilateral rotary nystagmus was also noted. The optic discs were atrophic, the edges being clear cut. Vessels of the fundi and the maculae were normal.

On the ninth day after admission to the Fountain Hospital he developed bronchopneumonia. He died 16 days later, at the age of 3 years and 2 months.

INVESTIGATIONS. C.S.F. examinations showed no abnormality and W.R. and Kahn tests were negative. An air encephalogram revealed internal hydrocephalus.

PATHOLOGICAL FINDINGS. The necropsy, on the day

after death, was done by the Coroner's pathologist. The cause of death was acute suppurative bronchopneumonia.

The fixed brain, asymmetrical due to the right hemisphere being slightly larger than the left, with the cerebellum and brain stem, weighed 915 g. (average normal for age is 1,141 g.). Radiographically, the ventricles were moderately distended; there was no evidence of calcification. The meninges over the frontal lobes and tips of the temporal lobes were opaque and congested. The superior and middle frontal, and the superior precentral sulci, were widened. The surface of the uncus was finely granular; the entire corpus callosum was very thin, being only 1 mm. thick in its thinnest part. The basal ganglia looked normal. There were widespread fine ependymal granulations of the lateral ventricular walls. The optic nerves were small and at the chiasma were 2·5 × 1·5 mm. (normal 4·7 mm. (Duke-Elder, 1932)), but other cranial nerves and the vessels at the base of the brain were normal.

HISTOLOGICAL FINDINGS. Coronal sections of the frontal, parietal and occipital lobes, the basal ganglia with temporal lobes, the mid brain, pons, medulla and cerebellum were embedded in celloidin and sections stained by the usual neuropathological procedures—Nissl, Heidenhain, H.V.G., Mallory's P.T.A.H. and Holzer. Paraffin and frozen sections were used when necessary for the Holzer, Kultschitzky-Pal, Bielchowsky, Turnbull and Scarlet R methods.

There were conspicuous structural changes in the cerebral hemispheres. Nerve cells were sparse in all regions of the cortex, being most marked in layer III. Surviving cells appeared normal in size and shape. Status spongiosus affected some cortical areas at the level of layer III. Perigyral gliosis was marked in the frontal, parietal and occipital lobes and to a much less extent around the uncus. Apart from shallow undulations of the surface of the uncus and this slight gliosis, there was no histological explanation such as granular atrophy to account for the curious naked eye granular appearances of the part.

The white matter in the parietal, temporal and occipital lobes was abnormally pale in sections stained by myelin techniques. Higher magnifications revealed various stages of degeneration of the myelin sheaths and breakdown such as tortuosity, focal ballooning, varicosity, uneven staining and beading. Astrocytes were increased throughout the white matter and there was a fine reticular fibrous gliosis in the corona radiata and the central core of white matter of the gyri of the frontal, parietal, temporal and occipital regions; it was densest in the tapetum. Lipid phagocytes were confined locally in a scanty fashion to the vicinity of blood vessels. There were no areas of localized softenings, tissue breakdown and cyst formation in the white matter. The arcuate fibres were involved to an equal extent with other white fibre tracts.

The thalamus, striatum and pallidum appeared to have a normal number of healthy looking cells and a normal amount of white matter. Fibrous gliosis was absent. Similarly the corpus Luysii and red nucleus were healthy.

Comparison of the mid brain section at the level of the superior corpora quadrigemina with a similar section

FIG. 1a.—Case 1, paucity of cells in the substantia nigra of one half of the mid-brain. H.V.G. ×6.

FIG. 1b.—Case 2, absence of cells in the substantia nigra. H.V.G. × 6.

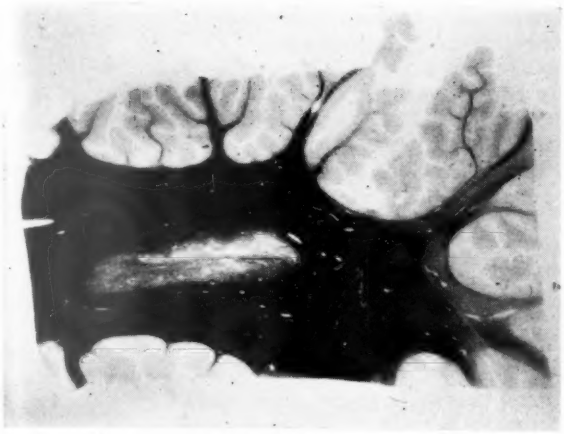

FIG. 2.

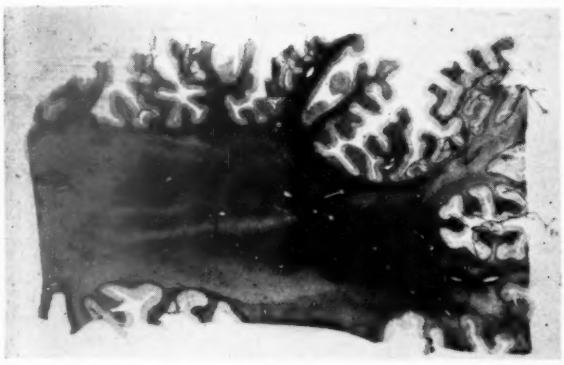

FIG. 3.

from a control brain (a child aged 18 months) revealed definite sparseness of nerve cells in the substantia nigra. Those cells present lacked pigment, a normal finding at this age, and were in three or four scattered groups (Fig. 1a). Status spongiosus affected the area. In other parts of the brain stem there was a normal complement of healthy looking cells in the olives pontine and cranial nerve nuclei. The pyramids were small and pale. Fibrous gliosis was present in the inferior olives and in their central core of white matter, hila and white fibres around their convolutions. A fine diffuse network of glial fibres was present throughout the reticular formation.

Periventricular gliosis was increased around the dilated ventricles. The ependyma was absent in places and replaced by ependymal granulations—a feature most marked in the fourth ventricle.

Cellular components of the cerebellum were fewer in numbers than normal. This was most obvious in the dentate nucleus but Purkinje and granular cells were also reduced in numbers. Pallor of the myelin was present in the central core of white matter of the dentate nucleus, and medullary white matter of the cerebellum and the central core of the folia and leaflets (Fig. 2). There were large globules up to 70 μ in diameter around several blood vessels which stained with the myelin stain. All parts of the cerebellum exhibited fibrous gliosis with an increase of glial cells; for instance, there were reticulated masses of fibres in the medullary white matter and folia (Fig. 3), and in the molecular, Purkinje and granular cell layers there were focal areas of perpendicular gliosis (Fig. 4).

The optic nerves were demyelinated and composed of a network of glial fibres surrounding lacunae from which the myelin sheaths had disappeared.

FIG. 4.

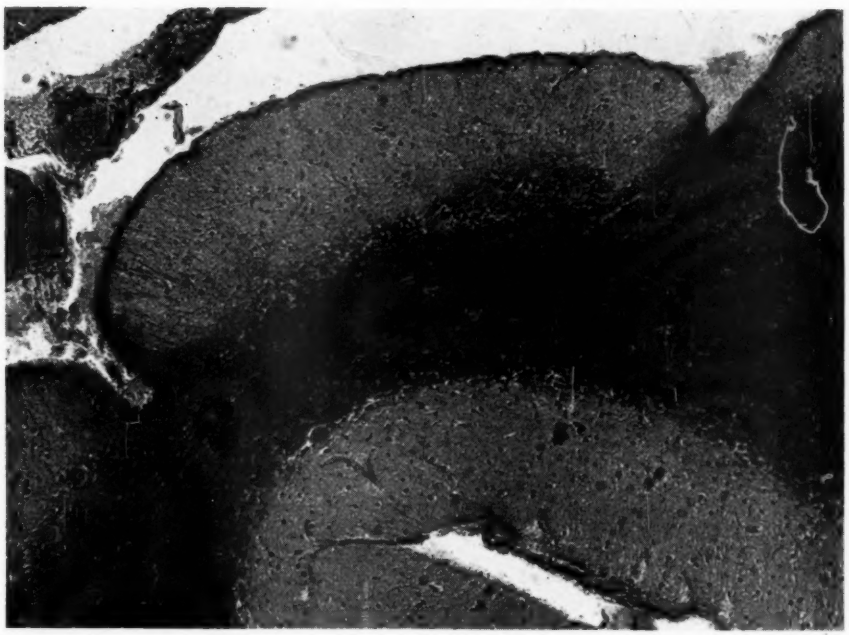

FIG. 2.—Case 1, pallor of the cerebellar white matter. Kultschitzky-Pal × 2½.

FIG. 3.—Case 1, gliosis of the cerebellar white matter. Holzer × 2½.

FIG. 4.—Case 1, foci of perpendicular gliosis in the molecular, Purkinje cell and granular cell layer causing puckering of the surface of the folia. Mallory's P.T.A.H. × 100.

Pia arachnoid vessels were congested. A fine picrophilic deposit was present under the pia in places. The pia arachnoid was thickened and fibrosed over the frontal region, but in other cases the membranes were normal.

Clear lacunae were present around many blood vessels, especially those in the grey matter and brain stem. In several instances similar spaces were filled by a fine picrophilic substance.

There was no evidence of lipoidosis, abnormal pigmentation or calcification.

Case 2.—Pregnancy was apparently normal, the child being delivered by caesarean section just before labour began. This operation was performed at the mother's request to avoid a possible birth injury—to which the elder brother's condition had been attributed. The birth weight was 8 lb. 15 oz. (4,040 g.). Discharge from the hospital was on the 21st day, normal progress apparently having occurred. At 7 weeks, he was admitted to hospital because he had started having epileptic seizures. They were tonic in type beginning with sudden jerks of the limbs after which the whole body stiffened. The face became cyanosed and frothing of the mouth occurred. These seizures persisted with increasing frequency and were triggered off by the slightest stimuli, especially during feeds. As in his brother, phenobarbitone seemed to have no effect on the course of the fits. Feeding difficulties were also present, and he suffered from severe constipation.

He was regarded as a normal baby up to 7 weeks old when the fits started. After that mental deficiency gradually became more and more obvious and by the time he was admitted to the Fountain Hospital at 15 months, he was a gross idiot. He lay inert in bed, in a sleep-like state most of the time. He appeared to be blind and was probably deaf, though he was thought to respond to the sound of a bell by momentarily widening his eyes and blinking. He failed to respond to any stimuli except painful ones to which he reacted by crying in a faint monotone. He was unable to suck, having to be fed slowly with a spoon; he had no grasp reflex and his developmental quotient was scored as less than one month, i.e. a little better than that of the elder brother.

CLINICAL FINDINGS. On admission to the Fountain Hospital he weighed 10 kg., height 75 cm. (normal for age and sex is 10·75 kg. and height 78·5 cm.). The head circumference was 45·6 cm. (normal for age and sex is 48 cm.).

At 7 weeks his head was noticed to be asymmetrical. The right side of the skull had a steeper contour than the left and the anterior fontanelle had closed by 15 months. The nose was flat and the eyes were slit-like. No teeth had erupted. His extremities resembled those of a young infant. The thumbs were flexed firmly within the palms of the hands. He was unable to hold up his head, to sit up or perform any other coordinated movements. The muscle tone was slightly increased. The Babinski sign was present bilaterally, though all the tendon jerks and abdominal reflexes were reported absent. His testicles were undescended (as was the case with the elder brother).

On the eighth day after admission to the Fountain Hospital, he suddenly collapsed with severe dyspnoea, with a high fever and signs of bronchopneumonia. He died two hours later, at the age of 16 months.

INVESTIGATIONS. At 7 weeks skull radiograph was normal. Subdural explorations revealed no haematoma. The optic discs were pale. C.S.F., serum chlorides and W.R. were all normal.

PATHOLOGICAL FINDINGS. The necropsy on the third day after death was performed by the Coroner's pathologist. Death was due to bronchopneumonia.

The fixed brain, asymmetrical due to the right hemisphere being slightly larger than the left, with the cerebellum and brain stem weighed 807 g. (average normal for age is 944 g.). Radiographically, the lateral ventricles were moderately distended; there was no evidence of calcification. The meninges were congested but not opaque. The superior frontal, superior precentral and cingulate sulci were widened. The corpus callosum was thinner than normal throughout its length; its mid part was 1 mm. thick. The surface of the uncus, as in the brother, was finely granular (Fig. 5). The basal

FIG. 5.—Case 2, the granular appearance of the surface of each uncus accentuated by a network of vessels.

ganglia appeared to be normal size. The ependyma was smooth. The optic nerves were small and at their approach to the chiasma were 2·75 × 2·0 mm. (normal 4 to 7 mm. (Duke-Elder, 1932)). The other cranial

nerves were normal and vessels at the base of the brain were normal.

HISTOLOGICAL FINDINGS. Coronal sections were prepared and stained as for Case 1. The findings in the cerebrum, brain stem, cerebellum and optic nerves were very similar to those of the brother, although there were some differences, notably in the extent of damage in the two cases.

The substantia nigra of Case 2 was more severely affected than Case 1 (Fig. 1b). Nerve cells were almost completely absent and those which remained were degenerated ghost forms. Unlike Case 1, similar changes to those in the substantia nigra were present in the corpus luysii. There was a condensation of dense glial tissue around the putamen of Case 2 (Fig. 6) in whose brain stem all parts were more gliosed than in the brother. Gliosis was particularly dense in the trapezoid bodies, the grey part of the reticular formation, the XII nerve nucleus, and in and around the inferior olives. Cerebellar involvement was less than in Case 1, for instance, the molecular, Purkinje and granular cell layers had escaped gliosis, although their numbers were reduced. The dentate nucleus and white matter were diseased

FIG. 6.—Case 2, glial tissue around the putamen. Holzer × 5.

in a similar manner to Case 1. Case 2 had no ependymal granulations, although periventricular gliosis was increased. The meninges were nowhere thickened. There was apparently less histological evidence to explain the curious naked eye appearances of the granularity to the surface of the uncus since perigyral gliosis was much less than in Case 1. The surface was definitely more undulant than usual and the hollows were occupied by congested meningeal vessels, otherwise the architectonics were quite normal.

Discussion

Cases bearing some similarity to these brothers have been described by Alpers (1931) and called 'diffuse progressive degeneration of the grey matter of the cerebrum'; Christensen and Krabbe (1949) who called their case 'poliodystrophia cerebri progressiva (infantalis)', and Ford, Livingston and Pryles (1951) who called the condition 'familial degeneration of the cerebral grey matter in childhood'. Wolf and Cowen (1956) included a case under the heading 'diffuse progressive cerebral cortical atrophy'. Their principal findings are listed in the Table.

Convulsions, the earliest clinical manifestations in our cases, commenced at 3 weeks (Case 1) and 7 weeks (Case 2) and were earlier in onset than those of other observers. It was possible that the illness occurred prenatally in Case 1 since hydramnios was associated with intra-uterine life from the seventh month. This accords with a view expressed by Christensen and Krabbe (1949) who thought that the disorganization of the cortical cellular layers in their case was congenital in origin although they could not exclude the possibility that it may have been a consequence of later degeneration.

Ataxia and choreo-athetoid movements present in some of the reported cases (see Table) were absent in the brothers. This was possibly due to the widespread lesions masking the expected clinical features.

Despite the patients' failure to pass any developmental milestones, there were features that the disease was progressive, borne out by the fits becoming more frequent and severe, increasing drowsiness and increasing paralysis of the limbs. This conformed with the findings of Christensen and Krabbe (1949) who found a series of features indicating postnatal progressive processes.

Birth trauma was an unlikely cause of the condition, especially in view of the extra care taken to prevent this in Case 2, and the lack of supporting pathological features such as ulegyria (cortical atrophy) and *état marbré* (marbling) the cause of which is often attributed to birth injury. Slight meningeal thickening and some ependymal granulations in Case 1 suggested an infective cause, but both these features were absent in the other child. Since the lesions in the two brains were so similar in other respects, it was felt that the basic cause of the

TABLE

COMPARISON OF CASES

DISEASES TO BE CONSIDERED IN THE DIAGNOSIS OF THE TWO PRESENTED CASES

Authors	No. of Cases Reported	Age at Onset	Clinical Features	Neuropathological Findings
Alpers, 1931 Diffuse progressive degeneration of the grey matter of the cerebrum	1	3 months	Convulsions, hyperkinesis, generalized rigidity, increased tendon reflexes, unable to hold up her head, died at 5 months	Defective cortical development, neuronal degeneration and astrocytic proliferation in cortex, striatum, pallidum and thalamus, cerebellum spared
Christensen and Krabbe, 1949 Poliodystrophia cerebri progressive (infantilis)	1	8 months	Delayed milestones and mental retardation and gradual deterioration of both mental and physical conditions Increasing spasticity and myoclonic contractions, abnormal tendon reflexes, paresis and ataxia, optic atrophy and probably deaf and dumb, dental anomalies up to four generations, died at 2½ years	Cerebral atrophy with secondary increase in microglia, whereas white matter was fairly well preserved, similar findings in basal ganglia, cerebellum and brain stem
Ford, Livingston and Pryles, 1951 Familial degeneration of the grey matter in childhood	4	Cases 1 and 2 6 years Case 3 6 months Case 4 4 years	Mental retardation, epileptic fits, myotonic and choreo-athetoid movements, increasing spasticity, hemiplegia and progressive dementia Cases 1 and 2 were sister and brother and maternal uncle died in status epilepticus	Cortical atrophy, destruction of neurones, proliferation of astrocytes, microglia and capillary proliferation and secondary myelin loss. Thalamus, corpus subthalamicum and substantia nigra, striatum, cerebellar cortex and dentate nuclei were degenerated
Wolf and Cowen, 1956 Diffuse progressive cerebral cortical atrophy	8	3 months to 2 years	Epileptic seizures, spasticity, mental retardation, blindness and spastic quadriplegia	Cerebral atrophy with loss of nerve cells; thalamus, cerebellum, corpus striatum, caudate and dentate nuclei and putamen affected (Some degeneration of posterior-column and spino-cerebellar tracts in spinal cord in one case)
Presented cases	2	At birth	Fits, blindness, hypertonus, nystagmus Babinski response variable, idiocy early in onset	Paucity of nerve cells in cortical grey matter, cerebellum and substantia nigra. Pallor of myelin corona radiata and cerebellum. Fibrous gliosis around inferior olivary nuclei, in tegmentum and in Case 2 around lentiform nucleus. Optic nerves pale and gliosed.

lesions had some other origin with perhaps secondary infection complicating Case 1; however, this was not proved during life by clinical investigations.

Two of the cases described by Ford *et al.* (1951) were half-sibs (brother and sister). Malamud and Cowen (1958) described findings in two male first cousins which they regarded as an unusual form of cerebellar ataxia transmitted by sex linked inheritance. Only one case was examined pathologically and features similar to some of those of the brothers were described, for instance, gliosis of the cerebellar folia, dentate nucleus, inferior olives, basal ganglia and optic tracts.

An appraisal of the clinical and pathological evidence and that of the reported cases suggested that the lesions in these brothers were probably determined prenatally. It was felt that genetic factors may be an important influence; though there was no proof of this, however, it would concur with our view from experience that there may be several forms of mental deficiency other than well-known conditions such as phenylketonuria, amaurotic idiocy and so forth, which may be caused by genetic factors.

'Degeneration of the cerebral grey matter', part of the descriptive name used by Alpers (1931), Christensen and Krabbe (1949), Ford *et al.* (1951) and Wolf and Cowen (1956) was too limiting in view of the changes in the cerebral white matter, the brain stem and cerebellum, and it seemed more appropriate, if the disease is the same, to call the condition familial diffuse progressive encephalopathy in childhood.

Summary

A disorder involving a diffuse progressive encephalopathy occurred in two brothers, beginning in the first possibly before birth and in the second around the time of birth.

A family study failed to reveal similar cases.

The main clinical features consisted of progressive mental deterioration, epileptic fits and increasing spasticity and paralysis. Both children became deaf and blind. Apart from slight nystagmus, there were no involuntary movements or other signs of a cerebellar disorder. Kyphoscoliosis and equino varus were present in both.

The principal neuropathological features were paucity of nerve cells in cortical grey matter, cerebellum and substantia nigra. There was pallor of myelin in the corona radiata and the cerebellum. Fibrous gliosis was present around the inferior olivary nuclei, in the tegmentum and in one case around the lentiform nucleus. The optic nerves were pale and gliosed.

Norms of weight, height and head circumference are quoted from *Studies of Child Health and Development*, Harvard School of Public Health, in Nelson's 'Textbook of Pediatrics', Philadelphia, 1959.

We are indebted to Drs. L. T. Hilliard and L. Crome, and many other colleagues at the Fountain Hospital for their help and advice.

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POSTNATAL PLASMA SHIFT IN PREMATURE INFANTS

BY

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(RECEIVED FOR PUBLICATION OCTOBER 28, 1959)

In the normal infant birth is usually followed by a substantial rise in the concentration of haemoglobin (Hb) and in the packed cell volume (PCV) of the blood, while the concentration of plasma protein tends to rise only slightly (Gairdner, Marks, Roscoe and Brettell, 1958). From these facts we have inferred that immediately following birth there is a loss from the vascular compartment of a large fraction, up to a quarter or more, of the circulating plasma.

We do not know the fate of the plasma lost from the vascular compartment, but we have suggested that the major changes which take place in the pulmonary circulation at birth might be expected to favour a shift of fluid from the circulation at this site. If so, then shift of plasma into the interstitial spaces of the lung might play a part in the pulmonary failure which so often overtakes the premature infant in the first few hours or days after birth. For this reason, we have extended our observations to premature infants to determine whether there is any relationship between the postnatal haemoconcentration effect and the development of pulmonary symptoms.

Material and Methods

Cord blood was obtained from 24 infants with birth weight of less than 2,500 g., of whom 22 were born vaginally and two by caesarean section. Maternal toxaemia was present in six cases. Neither the method of delivery, nor the presence of maternal toxaemia appeared to affect the results, and they have not been separately analysed here.

The cord was always clamped as soon as conveniently possible, both in vaginal and in caesarean deliveries. A blood sample was taken by puncture of the umbilical vein between placenta and clamp. Subsequent specimens were taken by insertion of a polyvinyl cannula (internal diameter 1·0 mm.) into the umbilical vein, or in a few cases by femoral vein puncture. Samples were taken into siliconized bottles containing ethylenediamine tetra-acetate as anticoagulant.

Hb concentration and PCV were estimated as described previously (Marks, Gairdner and Roscoe, 1955), in duplicate in most cases. Plasma protein concentration was estimated by the biuret method using 0·2 ml. plasma. The estimations required less than 2 ml. blood.

The infants were closely observed for signs of respiratory distress; those commonly observed were rapid moaning respirations, often with rib recession. Nine infants showed such signs and six of these recovered.

Three infants died at 20, 22 and 32 hours; all showed respiratory distress by five hours or earlier. At necropsy the lungs showed the picture of secondary atelectasis with hyaline membrane in all three cases, together with massive intra-alveolar haemorrhage in one case, and broncho-pneumonia in another.

Results

Change in Hb Concentration a Few Hours after Birth. A second specimen of blood was obtained from 24 premature infants at some time between one and eight hours after birth, in most instances about two hours after birth. The mean Hb was 17·9 g./100 ml. (S.D. 2·0) in cord blood and 19·4 g./100 ml. (S.D. 2·3) at one to eight hours. The difference of 1·5 g./100 ml. is just significant (P=0·05).

Fig. 1 shows the change in the Hb concentration shortly after birth related to the initial cord Hb.

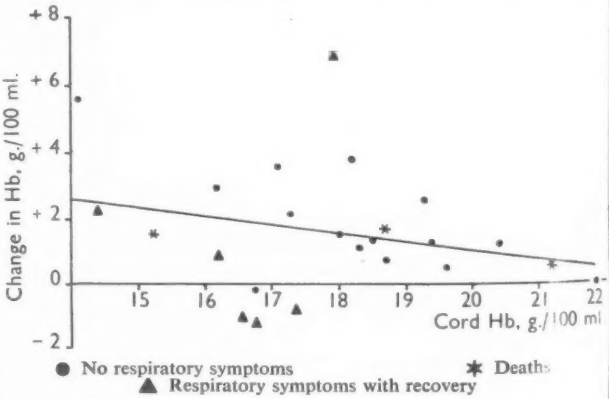

FIG. 1.—Relation of change in Hb level 1–8 hours after birth to initial (cord) Hb level, in 24 premature infants, of whom nine showed respiratory distress symptoms with three deaths. A regression line has been drawn, but the correlation coefficient is not significant.

There is some tendency for the change to be larger when the cord Hb level lies towards the lower side of normal, but the correlation is not significant (correlation coefficient −0·23).

The degree of postnatal haemoconcentration observed in the nine infants who subsequently developed respiratory distress, including the three who died, was similar to that in the remainder of the group.

Change in Mean Corpuscular Hb Concentration (MCHC) a Few Hours after Birth. Hb and PCV were estimated in cord blood and again in a second specimen taken between one and eight hours after birth, and Fig. 2 shows the percentage change in PCV compared with the percentage change in Hb concentration. Had the Hb concentration and

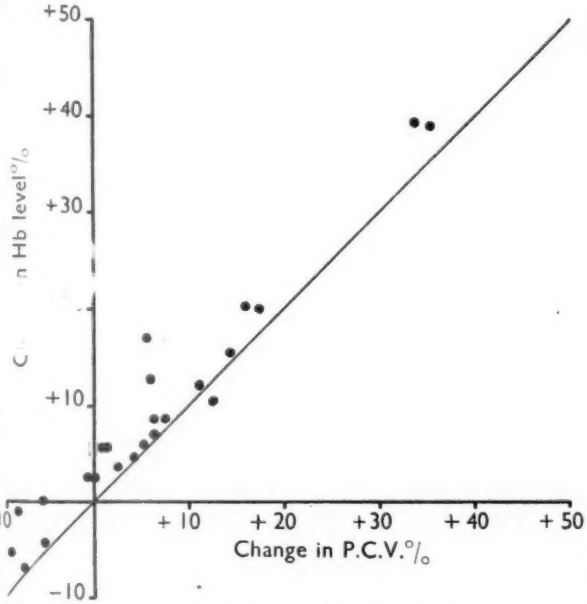

FIG. 2.—Relation of change in Hb level 1–8 hours after birth to change in packed cell volume, 24 cases. The line bisects the axes. Note that the change in Hb exceeds the change in PCV.

PCV moved strictly in parallel, the points would have been grouped about the straight line bisecting the axes. In fact, all but one point fall above this line showing that the rise in Hb concentration is proportionately greater than the rise in PCV. Since the ratio $\frac{\text{Hb concentration}}{\text{PCV}}$ defines the mean corpuscular Hb concentration (MCHC), these results indicate a postnatal rise in MCHC.

The mean MCHC of cord blood in the 24 cases was 32·3% and in blood at one to eight hours, 33·3%, a postnatal rise of 3%.

Change in Plasma Protein Concentration a Few Hours after Birth. Plasma protein concentration could not be measured in all cases, because findings were often invalidated by haemolysis, even a trace of which renders inaccurate measurements of plasma protein. We have not discovered means of avoiding this annoying tendency for blood samples taken in the early neonatal period to undergo haemolysis.

In the nine cases where full data were available, no consistent change in plasma protein concentration was found. The mean concentration in cord blood was 5·3 g. and between one and eight hours 5·2 g./100 ml. Four subjects showed decreases of up to 9%, one showed no change and four showed increases of up to 12%.

Discussion

The Postnatal Haemoconcentration Effect and its Relation to Pulmonary Failure in Premature Infants. Comparing the Hb concentration in blood at birth (cord blood) with that after birth (1-8 hours), our findings in premature infants show essentially the same changes in haemoconcentration as were previously found in normal infants (see Table).

TABLE

POSTNATAL CHANGES IN BLOOD IN NORMAL AND PREMATURE INFANTS

		No. of Cases	Cord Blood	At 1–8 Hours	Postnatal Change %
Normal	Hb, g.%	92	16·6	19·1	+16
	MCHC, %	92	32·3	33·6	+4
	Plasma protein, %	17	6·5	7·0	+8
Premature	Hb, g.%	24	17·9	19·4	+9
	MCHC, %	24	32·3	33·3	+3
	Plasma protein, %	9	5·3	5·2	−2

In our earlier paper we considered in turn the possible causes of the postnatal rise in Hb concentration as seen in normal infants, and arrived at the conclusion that it results from a reduction in plasma volume (Gairdner *et al.*, 1958). The same arguments and the same conclusion must apply equally to the present findings in premature infants.

The fact that while the concentration of Hb in the premature rises by an average of 9%, the concentration of plasma protein remains virtually unchanged, implies that the fluid leaving the vascular compartment contains about the same concentration of protein as does plasma. Thus we conclude that in premature infants as in normal infants, birth is often immediately followed by the loss of an appreciable fraction of the plasma from the vascular compartment.

As an instance of the magnitude the plasma shift may attain, details of one case are given. A 35-week

premature infant with a birth weight of 2,240 g. had a cord blood Hb level of 18·1 g./100 ml. and a PCV of 56%. At 8 hours the Hb level had risen to 25·2 g. and the PCV to 75%. It was formerly shown (Gairdner *et al.*, 1958) that the ratio

$$\frac{\text{Plasma volume at birth}}{\text{Plasma volume after birth}}$$

is given by

$$\frac{Hb_2\ (1-0{\cdot}83\ PCV_1)}{Hb_1\ (1-0{\cdot}83\ PCV_2)}$$

where the Hb level and the PCV are Hb_1, PCV_1 *at birth* and Hb_2, PCV_2 *after birth*. Inserting in this expression the values in our case, the ratio

$$\frac{\text{Plasma volume at birth}}{\text{Plasma volume after birth}} = \frac{1{\cdot}98}{1}$$

so that in this infant the plasma volume after birth was reduced by almost 50%.

In this series the magnitude of the postnatal plasma shift bears no relation to the development of respiratory distress (Fig. 1), so that the present study has provided no supporting evidence for the suggestion that plasma shift, if taking place mainly in the lungs, might cause pulmonary oedema and so lead to respiratory symptoms.

The postnatal rise of 3% in the MCHC is close to the figure found for normal infants, and implies that birth is followed by a shift of fluid from the red cells. The possible causes of this effect also have been discussed in our earlier paper.

Summary

In premature infants, as in normal infants, birth is frequently followed by a rapid rise in the Hb concentration, and in the packed cell volume of venous blood, while the mean corpuscular Hb concentration of the red cells increases.

The cause of these changes is considered to be a considerable loss of plasma from the vascular compartment, and a small shift of fluid from the red cells.

The site at which the plasma leaves the vascular compartment remains undecided. It was suggested that the shift might take place particularly from the pulmonary circulation and so contribute to the development of pulmonary oedema and respiratory failure in the premature infant, but the development of respiratory distress in the premature infants studied could not be shown to be related to the magnitude of the plasma shift.

One of us (A.C.L.C.) was in receipt of a grant from the Elisabeth Storey Fund.

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ABSORPTION OF RADIOACTIVE IRON BY ANAEMIC INFANTS

BY

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(RECEIVED FOR PUBLICATION SEPTEMBER 25, 1959)

The oral administration of iron to anaemic infants often fails to restore the haemoglobin level as rapidly as it would in an adult. The reason for this failure could be either failure of absorption or failure to utilize the iron which had been absorbed, or deposition of all the iron in the tissue stores without any being incorporated in the haemoglobin. It was therefore decided to study the absorption and utilization of iron in anaemic infants and children using tracer quantities of the isotope ^{59}Fe administered orally.

Method

Three control and six anaemic infants and children were studied. Blood and marrow studies were made in all cases. The anaemic cases had a haemoglobin range of from 3·0 to 9·6 g.

Controls	% of Dose Appearing in Blood	% of Absorbed Iron Appearing in Blood	% of Dose Recovered in Stool	% of Dose Absorbed	Haemoglobin (g.)
J.N.	40·0	63·5	37	63	11·0
F.D.	3·7	5·8	37	63	10·8
J.F.	8·7	21·7	60	40	10·8
Anaemic Patients					
W.A.	4·0	40·0	90	10	9·6
I.M.L.	31·0	50·0	62	35	8·5
F.C.D.	6·0	40·0	85	15	8·4
J.M.	4·0	11·1	64	36	9·6
M.D.	15·4	16·7	8	92	4·8
P.S.	20·0	23·2	14	86	3·0

Two microcuries of ^{59}Fe were given in 5 ml. of water which contained 100 mg. of ferrous sulphate or 30 mg. of iron. After oral administration of the dose, the faeces were collected for five days, and bulked. They were then homogenized in a mixer and an aliquot was counted in a well-type scintillation counter. Blood samples were taken on four occasions during the next fortnight into a mixture of potassium oxalate and sodium fluoride anticoagulant, and counted in the same apparatus. An aliquot of the dose was diluted and counted as a standard, so that the percentage of the dose excreted in the faeces and circulating in the blood stream could be calculated.

Blood volumes were determined in each case by the Evans blue technique (Muldowney, 1957). The highest figure obtained from the blood was added to that from the faeces, and the remaining percentage of the original dose was considered to have entered the tissue stores. In view of the difficulty of performing external body counting tests upon small infants this estimation was not attempted (Wetherley-Mein, Hutt, Langmead and Hill, 1956).

Results

The relation of four factors was studied, the degree of anaemia, the level of ^{59}Fe in the blood, its absorption and its utilization.

Blood Levels of ^{59}Fe. Radioactivity was present in the blood in the first examinations (Fig. 1), on

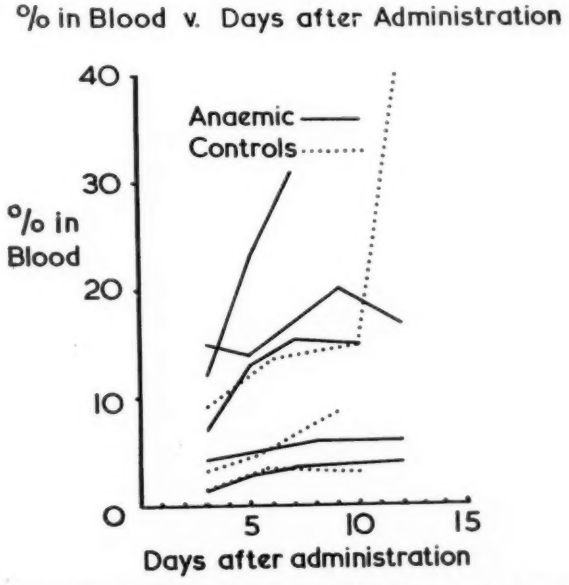

FIG. 1.—Showing rise in the percentage of the isotope administered appearing in blood up to a fortnight after administration.

the third day and usually continued to rise steadily until the seventh day. This indicates that oral radioactive iron in tracer doses is rapidly incorporated in haemoglobin. This is in agreement with the findings of other workers.

Effect of Anaemia. The final level reached is directly related to the degree of anaemia present (Fig. 2) and the more severe the anaemia the higher the final level of the isotope in the blood.

Preliminary experiments were conducted using the blood level as a guide to absorption, but it now became apparent, as it had to other workers (Josephs, 1958) that blood levels are reliable as a measure of absorption only if utilization is complete, and this only occurs in the anaemias which follow haemorrhage and in the iron deficiencies of adults. Faecal excretion was therefore also estimated to give an iron balance (Dubach, Callender and Moore, 1948).

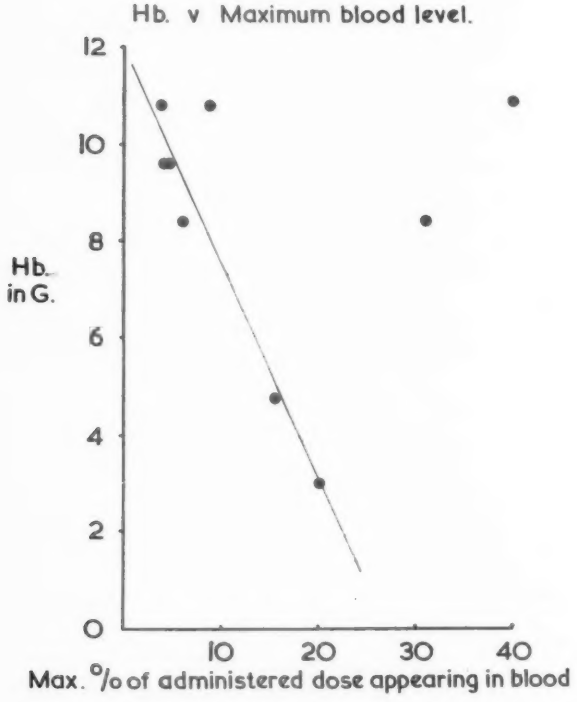

FIG. 2.—Showing that the highest percentages of administered isotope detected in the blood were usually associated with the lowest haemoglobin levels.

Absorption. This was measured from the faecal excretion which was 37-60% of the dose administered in the controls, and 8-85% in the anaemic cases. The remainder of the dose administered which was not recovered in the faeces, was assumed to have been absorbed. This gave absorptions in the controls of 40-63% with a mean of 49%, and in the anaemic cases of 10-92% with a mean of 45%. These wide variations are in accord with the findings in the literature, where absorptions in controls vary from 1·5-6·5% to 17-69% (Peterson and Ettinger, 1953; Bothwell, Mallett, Oliver and Smith, 1955, quoted from a table by Josephs, 1958).

Inspection of the levels in the anaemic cases (Fig. 3) suggests that there may be two types of anaemic child represented, one with a low absorption and one with a high absorption. This is supported by the fact that the two cases with high absorptions also attained high blood levels of the isotope.

The effect of anaemia upon absorption is considered by most workers to produce increased absorption, but in the present series this was only observed in the two cases in which the diet had been deficient, and there was a decrease in the other cases as compared with the controls.

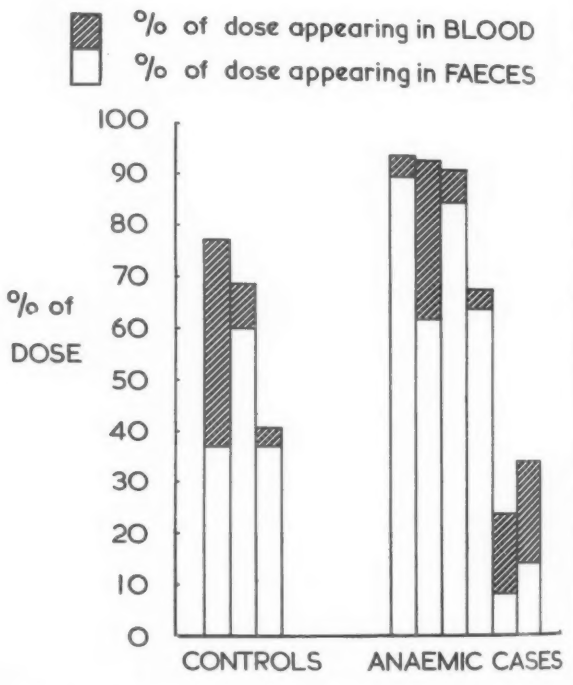

FIG. 3.—Showing the percentages of the isotope recovered from blood and faeces respectively.

Fate of Absorbed Iron. Once iron has been absorbed it may pass either to the tissues or be utilized in haemoglobin formation. Consequently a study of the factors likely to affect this distribution was made.

Level of Isotope in the Blood. There is a direct relationship between this and the utilization of the absorbed iron. The higher the total uptake of ^{59}Fe the higher the percentage utilization of the absorbed iron (Fig. 4).

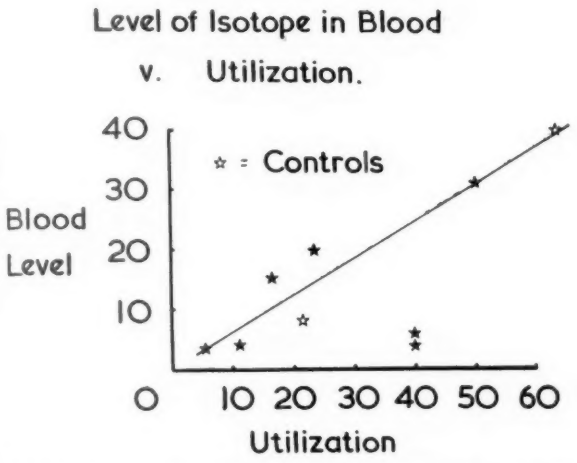

FIG. 4.—The relation between the amount of isotope appearing in the blood and the percentage of the iron absorbed which was utilized for haemoglobin formation.

Anaemia. This did not appear to affect directly the percentage utilization of absorbed iron.

Absorption. This on the other hand did show a slight relationship, a greater percentage of the absorbed iron being used for haemoglobin when the total absorption was low (Fig. 5).

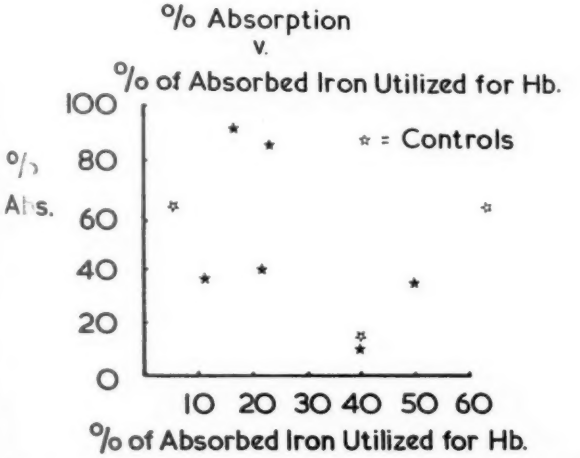

FIG. 5.—Demonstrates the percentage of iron, which, having been absorbed, is used for haemoglobin formation in relation to the total absorption of iron.

In assessing these results it is seen that radioactive iron enters the haemoglobin rapidly and rises to a steady level in about a week. The level ultimately attained, and the percentage of absorbed iron utilized, appear to depend upon the degree of anaemia rather than upon the total amount of iron absorbed. This is also suggested by the slightly higher utilization which occurs in cases of low absorption.

In the two types of anaemia which we have postulated in children, the high absorption and also the anaemia of one type, are both probably the result of depleted body iron stores, while in the other, the stores are probably normal, and the anaemia due in part to impaired absorption.

Discussion

The first investigations of anaemia in infancy showed that the blood picture was similar to that of iron deficiency anaemia in adults. This was the finding in all the anaemic cases of the present series who had hypochromia and microcytosis with the haemoglobin falling much lower than the red cells. Early studies of the effect of giving oral iron to these patients did not show as good results as were obtained in adults. There were in consequence many iron balance experiments performed (McCance and Widdowson, 1938; Hutchison, 1937) all of which showed that much more iron was absorbed than appeared in the red cells and that very little iron was excreted. It was deduced from this that large doses of iron were required for therapy. Studies of the plasma iron made about this time showed that it existed separately from the haemoglobin iron, and that it rose rapidly after ingestion of iron (Moore, Arrowsmith, Welch and Minnich, 1939).

Radioactive iron (Hahn, Bale, Ross, Balfour and Whipple, 1943) was given in tracer doses to dogs and was shown to be absorbed rapidly. This appeared to conflict with the results of the balance experiments but it is now thought that balance experiments conducted over a long period are not strictly comparable with those which study the effects of a single tracer dose. Clinical use of this method demonstrated that anaemic adults had higher absorptions than normal persons (Dubach *et al.*, 1948). The appearance of tracer doses in the blood was the method which was employed in the preliminary experiments of the present series but it became apparent that this was a measure of iron absorption, only if all the iron was utilized for blood production, and this was manifestly not the case (Jeffrey, Freundlich, Jackson and Watson, 1955). It has been shown in adults that this only occurs

after haemorrhage and in iron deficiency anaemia (Josephs, 1958). Balance experiments, in which the faeces were also estimated, were then introduced, and this was the method which we decided to employ. The uptake of intravenous doses of ^{59}Fe has also been studied by some workers (Dubach, Moore and Minnich, 1946) and is found to be increased if the iron stores are deficient, but the method would be difficult to use in children, and the placing of counters over the viscera would be inconvenient in infants.

Studies in children show that absorption is more complete than in adults (Darby, Hahn, Kaser, Steinkamp, Densen and Cook, 1947) and that it is more complete at 7 years than at 9 years. Contrary to former beliefs, absorption does occur at birth, but it may well be that utilization is slower (Oettinger, Mills and Hahn, 1954). Coeliac disease is associated with much impairment of absorption (Badenoch and Callender, 1954). We found this increase in absorption in childhood and we also found considerable variation between individual children. This has been found in the same patient on different occasions by some observers (Smith and Mallet, 1957).

Three sources of iron exist for children: the iron stores laid down at birth; the iron in the food; and therapeutic iron. The birth stores can be calculated, and may be deficient in small infants who grow rapidly, and in whom both tissue and haemoglobin iron may be inadequate in total quantity to supply the demands of growth, almost all of which have to be supplied from the iron present at birth (Smith, Rosello, Say and Yeya, 1955; Hahn *et al.*, 1951).

The food iron is probably adequate in artificially fed infants, since Feuillen and Plumier (1952) have shown that iron is acquired from utensils in the process of preparing the feed. Detailed studies of the absorption of food iron by children using ^{59}Fe have been made by Schulz and Smith (1958a) and they have again found greater, but variable, absorption of iron in children. They also studied the absorption of therapeutic iron (Schulz and Smith, 1958b) and found that anaemic children absorbed more than normal children and normal children more than normal adults, who are generally considered to absorb about 10% of the dose given. Their figures are lower than the present series in some instances, but other authors find higher rates. It is suggested that the present figures indicate two different types of anaemia in children, the one associated with a high uptake and the other with a lower figure. The possible sources of anaemia in childhood are: deficient stores at birth, or undue demand upon those stores, or impaired absorption. It would appear that the production of haemoglobin and the rate of absorption are not closely related. Provided sufficient iron is available haemoglobin formation will occur. The two variables are the amount absorbed, and the retention and release of this iron by the tissues. Tissue store iron appears to be in two forms (Neerhout, Armstrong, Schulz and Smith, 1958), the one available for haemoglobin synthesis and the other not available. What the factor may be which determines availability has not been determined (Smith *et al.*, 1955).

It appears that there may be two types of anaemia in small children, one associated with impaired absorption and slightly impaired utilization but normal tissue stores, and the other with depleted tissue stores which take up iron with great avidity, and utilize it with increased rapidity for haemoglobin synthesis.

Summary

The absorption and utilization of iron in anaemic infants and children was studied using tracer quantities of the isotope ^{59}Fe.

It is suggested as a result of these investigations, that there may be two types of anaemia in children, the one associated with a low absorption and the other with a high absorption.

The chief factor regulating the appearance of radioactive iron in the blood appears to be the degree of anaemia, and the chief factor regulating absorption, the state of the body stores.

The author wishes to express his thanks to the Regional Physics Department of the Western Regional Hospital Board for the supply of the isotope, and to Dr. M. M. Bluhm and his colleagues of that department for a great deal of technical assistance.

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APPENDIX

Clinical Details of Cases Studied

Controls

J.McN., aged 5 years, was admitted with tuberculous meningitis from which he made a good recovery. He was under treatment with P.A.S. and I.N.A.H. at the time of the observations, and his haemoglobin was 11 g. His birth weight was 6 lb. and his weight at the time of the experiment was 40 lb. His diet appeared to have been adequate.

F.D., aged 13 months, was a microcephalic admitted with bronchitis, his physique was normal and his intelligence only moderately impaired. His weight was 16 lb. and his birth weight was 6 lb. There was no obvious evidence of malnutrition and he took his feeds well, but it was possible that having been backward, feeding may have been difficult and therefore inadequate. His haemoglobin was 10·8 g. at the time of the experiment which was started on the seventh day after admission.

J.F., aged 2 years, was admitted with a respiratory infection. She weighed 28 lb. and her birth weight was 7 lb. Her diet may have been inadequate, since mixed feeding was not instituted until 1 year of age.

Anaemic Cases

I.Mc.L., aged 14 years, was first admitted at 7 years with pallor and was found to have an iron deficiency anaemia with a haemoglobin of 2·5 g. No adequate cause for this was found despite extensive investigations. The condition responded to oral iron but recurred on several occasions. Home conditions were poor and the diet was probably inadequate. This case differs somewhat from the others and may be considered atypical. His haemoglobin at the time of the experiment was 8·5 g.

F O'D., aged 18 months, was admitted on account of an upper respiratory infection and was found to have a haemoglobin of 8·4 g. His anaemia appeared to be due to three things: the fact that he was a premature baby weighing 3 lb. 11 oz. at birth, an attack of pneumonia at 6 months and delay in commencing mixed feeding until 1 year.

J.M., aged 12 months, was admitted on account of infantile eczema and transferred to the paediatric unit because of a cold in the head. His haemoglobin was 9·6 g., he weighed 20 lb. and his birth weight was 8½ lb. He had no previous history of infection and the only factor to which his anaemia could be attributed was the difficulty in feeding sometimes encountered in cases of infantile eczema.

W.D., aged 18 months, was admitted on account of stomatitis. Her weight was 23 lb. and her birth weight 7 lb. She was found to have a haemoglobin of 9·6 g. The cause of her anaemia was almost certainly nutritional as home conditions were poor.

The two remaining cases were those with the high uptakes and utilization.

M.D., aged 11 months, was admitted on account of her pallor. Her weight was 23 lb. and her birth weight 6¾ lb. Her haemoglobin on admission was 4·8 g. and the blood picture suggested a very severe iron deficiency. The cause of the anaemia in this case was almost certainly dietetic since she had been very difficult to feed. The response to oral treatment was immediate.

P.S., aged 6 years, weighed 31 lb. with a birth weight of 6 lb. He was admitted on account of pallor and his haemoglobin was 3·0 g. on admission. He was a very wilful child who refused to eat meat in any form, and it was obvious that the largely carbohydrate diet upon which he had been fed, was the cause of his anaemia. His response to oral iron was immediate.

HAEMOGLOBIN 'BARTS'— A RARE ABNORMALITY IN THE NEWBORN

BY

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(RECEIVED FOR PUBLICATION DECEMBER 9, 1959)

The study of qualitative abnormalities in haemoglobin is of fairly recent date. Two normally occurring haemoglobin variants have, however, been known for a long time: adult haemoglobin (Hb A) and foetal haemoglobin (Hb F) (Körber, 1866). They can be distinguished by alkaline denaturation, a test which has become routine practice in neonatal paediatrics (Singer, Chernoff and Singer, 1951).

About 10 years ago sickle cell anaemia was found to be due to an abnormal haemoglobin, now known as Hb S, which differs chemically from normal and is distinguished by its low solubility in the reduced state (Pauling, Itano, Singer and Wells, 1949). This decreased solubility implies a tendency to 'crystallization' (more correctly: conversion to semisolid gel) within the erythrocyte and is the cause of its sickle shape.

In the years that followed a great number of abnormal haemoglobin variants were detected, mainly among non-European people. Some of these are of great clinical significance, others are chiefly of genetic and anthropological interest. These variants were designated by the letters of the alphabet more or less in chronological order of detection.

By 1958 progress in this field had gathered so much speed, that confusion in nomenclature was likely to arise. Also, it could be foreseen that the letters of the alphabet would not suffice for all haemoglobin variants. So, when Ager and Lehmann (1958) detected a hitherto unknown abnormal haemoglobin, they named the new variant after the hospital in which the investigation had been carried out: Haemoglobin 'Barts'. This pigment was present with both Hb F and Hb A in the blood of an infant of mixed West Indian ancestry. Subsequently, about 30 infants with haemoglobin 'Barts' have been detected (Lehmann, 1959) in Mediterranean and non-European countries. This article records the second case observed in Great Britain.

Case Report

The infant's mother, I.B., aged 37 years, is a West Indian woman of negro stock. Before coming to England in 1956, she had five children born in Jamaica, of whom three are still alive. She had been married twice, the first husband, a 'white man', being the father of the first child only. The four other children had a Jamaican father.

The second of these five children died at the age of 9 days; the cause of death is not known. The fifth child was born prematurely and died when 3 days old. She does not know of any blood disease among her children, or any other members of her family.

In this country I.B. contracted a third marriage, also to a West Indian. His skin is of the same dark colour as that of I.B., but his features are not typically African and suggest the possibility of some Asian ancestry.

I.B. conceived in 1958, the date of expected delivery being June 14, 1959. The pregnancy progressed normally until 26 weeks when she had an episode of abdominal pain and vaginal bleeding. Further episodes of ante partum haemorrhage followed, necessitating admission to hospital. There, the placenta was found to be low lying, but was not considered to be praevia.

Surgical induction at 38 weeks was followed on May 27 by normal delivery of a female infant, weighing 7 lb. (3,170 g.) and measuring 20 in. (50 cm.). Her condition was only fair and in spite of the dark pigmentation the theatre sister noticed her pallor and commented on it.

Cord blood examination was carried out by the regional blood transfusion laboratory under the direction of Dr. W. Weiner, and gave the following results: blood group A, rhesus negative, direct Coombs test negative, bilirubin 0·6 mg./100 ml.

The next day the baby's capillary haemoglobin was estimated to be 94% (13·9 g.). This relatively low value was thought to be due, possibly, to transplacental blood loss. No physical abnormality was found and progress seemed to be satisfactory.

When the baby was 6 days old marked pallor and lethargy were noticed. The spleen was enlarged, but not the liver. There was no evidence of any haemorrhagic diathesis. In view of the baby's parentage it was regarded as essential to exclude sickle cell anaemia and to carry out further investigation.

Laboratory Investigation. Blood examinations were limited by the difficulty of venepuncture and had to be spread over a relatively long period.

The haemoglobin level fell from 10·8 g. (73%) on June 1, at the age of 6 days, to 8·6 g. (58%) on June 12.

A full blood count on June 16 yielded the following results: Hb 9·3 g. (63%); R.B.C. 3,580,000; W.B.C. 9,700; P.C.V. 31·5 ml.; M.C.V. 88 cμ; M.C.H.C. 30·5%.

Reticulocyte counts varied between 0·2% and 3%.

A stained blood film on June 3 revealed numerous target cells and a small number of microspherocytes; this finding was repeatedly confirmed on subsequent examinations (Fig. 1).

Sickle cells were not found in sealed wet blood film preparations, either with or without reducing agent. No inclusion bodies were seen in the red cells after 'cold incubation' with cresyl violet solution.

Haptoglobin was present in the serum. The serum iron on August 7, was 0·059 mg./100 ml.

Haemoglobin electrophoresis was carried out by Dr. H. Lehmann who demonstrated the presence of Hb 'Barts' as well as Hb A and Hb F (Fig. 2). This was confirmed on subsequent examinations.

INVESTIGATION OF THE MOTHER. A full blood count was done on June 8, with the following results: Hb. 12·0 g. (81%); R.B.C. 4,390,000; W.B.C. 5,000; P.C.V. 43 ml.; M.C.V. 98 cμ; M.C.H.C. 28%.

FIG. 1.

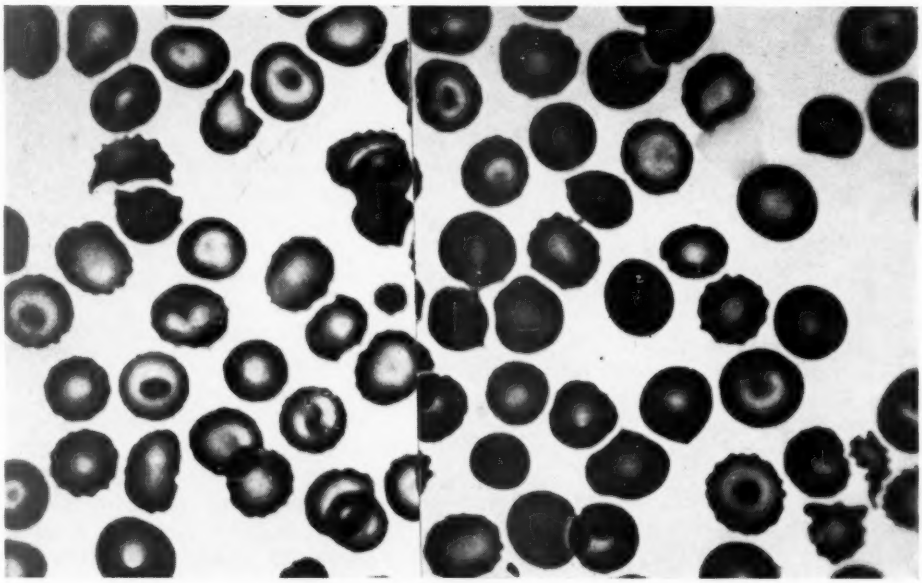

FIG. 1.—Composite picture of a blood film having numerous target cells and occasional microspherocytes.

FIG. 2.

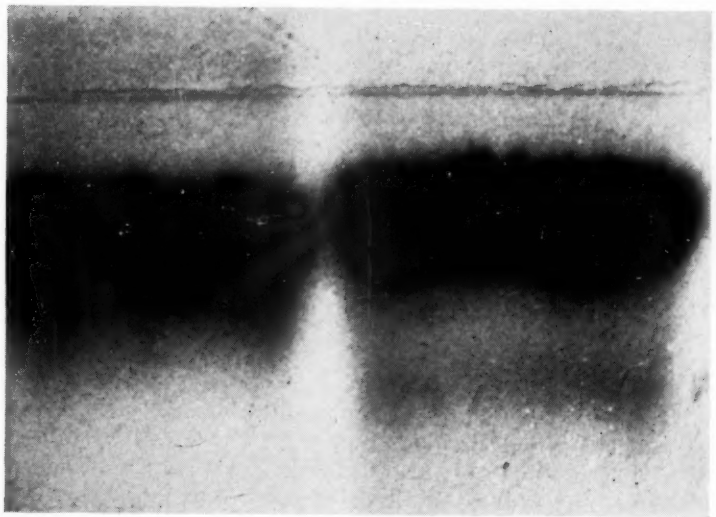

FIG. 2.—A normal (AA) compared with Baby B. Note 'fast' Hb in baby.

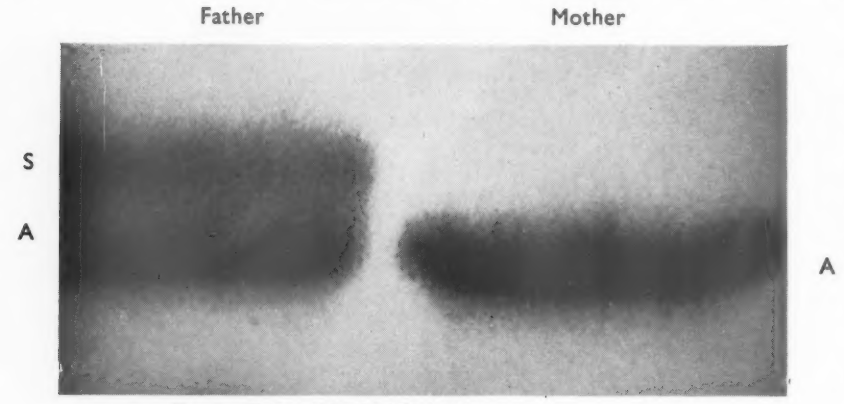

FIG. 3.—Father (AS), Mother (AA).

The stained film showed moderate regenerative activity consistent with recovery from a mild anaemia of pregnancy. No sickle cells were found. The serum iron level was 0·092 mg./100 ml.

Haemoglobin electrophoresis revealed Hb A only (Fig. 3).

INVESTIGATION OF THE FATHER. Full blood count revealed Hb 14·0 g. (95%); R.B.C. 5,700,000; W.B.C. 7,000; P.C.V. 46 ml.; M.C.V. 81 cμ; M.C.H.C. 30%.

Reticulocytes 2%. Sickle cells were found to be present after incubation with sodium bisulphite, in very large numbers.

Serum iron level 0·141 mg./100 ml.

Haemoglobin electrophoresis clearly demonstrated the presence of Hb S, as well as Hb A. The father was, therefore, confirmed as a heterozygous carrier of the sickle cell trait (Fig. 3).

Further progress. Baby B. was in reasonably good health when discharged from hospital on June 21. The haemoglobin level was then 9·0 g. (61%). The infant was seen repeatedly in out-patients and found to make satisfactory progress, but the haemoglobin level was dropping and on August 11 was as low as 7·1 g. (48%). Anti-anaemic treatment, including iron, folic acid and ascorbic acid was given. At the age of 15 weeks the total haemoglobin was 8·6 g. (58%) and haemoglobin 'Barts' was no longer demonstrable.

The infant was last seen on September 22; she was then nearly 4 months old and in good general health. The haemoglobin had risen to 9·8 g. (66%), but the blood picture was still hypochromic and microcytic. Target cells were still present and the osmotic resistance of the red cells was raised. Haemoglobin 'Barts' was absent from the electrophoretogram, but Hb F was still present, accounting for 6·8% of total haemoglobin.

Discussion

Anaemia in the new-born period can have many causes including prematurity, infection, maternal deficiency states, blood loss and haemolysis. In the present case, a contributory action of maternal deficiency anaemia and foetal blood loss cannot be excluded. The presence of large numbers of target cells is, however, strongly suggestive of a primary abnormality of the red blood cells whilst a small number of microspherocytes may be consistent with the haemolytic character of the process.

This anaemia was present from birth: the haemoglobin reading of 94% on the first day of life is definitely low. Moreover, pallor was noticed at birth.

The characteristic properties of haemoglobin 'Barts' were summarized by Lehmann and his colleagues (Ager, Hunt, Kohler and Lehmann, 1959). Here we draw attention to only some of its peculiarities:

(1) Both in the process of electrophoresis and of chromatography 'Barts' is one of the fastest moving haemoglobin variants so far known. Its position relative to other haemoglobins varies with the particular method used and with the *p*H of the buffering medium.

(2) Spectroscopically, 'Barts' is closely similar to foetal haemoglobin and shows the tryptophan band, which is characteristic of Hb F.

(3) Hb 'Barts' is less resistant to alkali denaturation than Hb F, but more so than Hb A.

(4) Hb 'Barts' tends to disappear, with progressing age, from the infant's blood much in the same way as 'normal' foetal haemoglobin does.

An apparent exception to this last-mentioned rule was recently discovered in a child whose 'Barts' had persisted beyond infancy. This child was found to be homozygous for thalassaemia (Choremis, Zannos-Mariolea, Ager and Lehmann, 1959).

Heredity. As haemoglobin 'Barts' is associated with infancy, there is no hope of finding any evidence of it in the parental electrophoretogram. Genetic investigations, which play so great a part in the study of other haemoglobinopathies, have so far failed to yield any positive results. This does not imply that we shall necessarily have to wait until those few infants with 'Barts', who are known at present, reach the reproductive age. Genetic information may be forthcoming from observation of their younger siblings. Where, in addition to true sibs, half-brothers and half-sisters are available for investigation, the possibilities of study are wider. In the present case history, I.B. with her three sets of

families almost fulfilled conditions designed for laboratory experiments and our regret of not being able to investigate her previous children is so much greater. We shall, of course, try to keep her under observation in any future pregnancies.

The finding of a heterozygous sickle cell trait in the father is an interesting observation, but in the light of our present knowledge this fact is unconnected with the infant's haemoglobinopathy.

Summary

Haemoglobin 'Barts' was found in the blood of an anaemic West Indian newborn girl. No evidence of this abnormal haemoglobin variant was found in either parent, but the father was heterozygous for Hb S. By the age of 15 weeks 'Barts' could no longer be demonstrated in the infant's electrophoretogram. This is the second case found in this country.

This paper could not have been written without the generous help given by Dr. Hermann Lehmann, who not only carried out the crucial diagnostic tests, but also guided us in the investigation and instilled into us some of his own enthusiasm. We are indebted to Dr. Ben Wood for permission to publish and to Dr. M. J. Meynell for help and advice. We owe thanks to Mr. W. R. Lea, F.I.M.L.T., for the microphotograph of Fig. 1. and to Mr. William Johnson, F.I.M.L.T., who took great pains in performing most of the routine examinations.

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SYSTEMIC LUPUS ERYTHEMATOSUS IN PREGNANCY WITH HAEMOLYTIC ANAEMIA, LEUCOPENIA AND THROMBOCYTOPENIA IN THE MOTHER AND HER NEWBORN INFANT

BY

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(RECEIVED FOR PUBLICATION SEPTEMBER 17, 1959)

Pregnancy in a patient with systemic lupus erythematosus is not extremely rare. However, very few reports dealing with the simultaneous occurrence of the disease or some of its manifestations in the mother and her newborn infant have been published. In the University Hospital, Oslo, we have observed a young woman with subacute systemic lupus erythematosus, whose newborn son for some time after birth presented haematological changes similar to those of his mother, probably due to passage of antibodies across the placental barrier.

Case Report

A housewife, 29 years of age, developed generalized lymphadenopathy, leucopenia and elevation of the erythrocyte sedimentation rate in February, 1958, during her fourth pregnancy. She had had an abortion in 1952 and a miscarriage in 1957. In 1953 she gave birth to a child who is living and well. In January, 1958, she was inoculated with BCG vaccine because her husband had contracted a tuberculous infection. She remained in fairly good condition until the beginning of July, 1958, when proteinuria, haematuria and anaemia developed. She was then admitted to the local hospital, where normal, spontaneous delivery took place on July 14, 1958.

Following delivery the patient developed a high, fluctuating fever which was not influenced by treatment with antibiotics in large doses. Her general health was poor and she suffered from pains in the chest and shoulders. Marked leucopenia with moderate eosinophilia was present. The haemoglobin dropped to about 7 g. %, and there were obvious signs of increased haemolysis: reticulocytosis and a positive Coombs test. Two blood transfusions had only transient effect and she was transferred to Medical Department A, University Hospital, Oslo, on October 4, 1958, while her 12-week-old infant was admitted to our department.

On admission she was in poor condition with high fever, emaciation and pallor. Her haemoglobin level was 7 g. %, but there were no longer signs of increased haemolysis. The Coombs test was only weakly positive. A weak red cell antibody, probably of the 'cold' type, could be demonstrated in her serum. She still had a persistent leucopenia with a minimum white cell count of 1,500 per c.mm. There were 171,000 blood platelets per c.mm. Erythrocyte sedimentation rate remained high, up to 133 mm., during her stay in the hospital. Her urine contained about 0·1% protein. Electrophoretic determination of the serum proteins showed a marked decrease in albumin (1·8 g. %), and a considerable increase in gamma globulin (3·3 g. %). Typical L.E. cells could be demonstrated and a diagnosis of subacute systemic lupus erythematosus was made. Under treatment with corticosteroids she made good progress, and was discharged on November 19, 1958. She is now receiving 10 mg. prednisone daily as a maintenance dose and is able to do her housework.

Her newborn infant looked somewhat pale at birth but otherwise appeared normal. He seemed to thrive fairly well on cow's milk during his first weeks of life. Because of the mother's illness he remained in the local hospital. After a few weeks his paleness attracted the nurse's attention. However, haematological studies were not performed until he was two months of age, when his general health seemed to be deteriorating. His haemoglobin level was then found to be 3·3 g. %; a few days later it was 2·5 g. %; erythrocytes 1·23 m./c.mm.; reticulocytes, 22·8%; leucocytes 1,800/c.mm. Bone marrow smears showed marked erythroid hyperplasia. Within two weeks five transfusions of whole blood had to be given, 500 ml. in all, but there was only transient effect on the haemoglobin level. A Coombs test, performed after the first blood transfusions were given, was equivocal.

He was transferred to the University Hospital, Oslo, on October 4, 1958, when 12 weeks old. He was slightly jaundiced with serum bilirubin 2·4 mg. %. His spleen was moderately enlarged. He had just received a blood transfusion, which had brought his haemoglobin up to 10·3 g. %. The white cell count had risen to 5,900,

the differential count was normal, blood platelets 114,000. L.E. cells could not be demonstrated. The Coombs test was now negative.

In three days his haemoglobin dropped to 5·8 g., and his reticulocyte count rose to 13·3%. He was given a transfusion of 100 ml. whole blood, but three days later his haemoglobin level had once more fallen to 5·6 g. On October 11, treatment with prednisone was begun. He was given 10 mg. per day in divided doses. Within two weeks the blood picture had become completely normal. The dosage of prednisone was gradually reduced and the medication was terminated on November 10, 1958, since when he has remained quite well, with a normal blood picture.

Except for the haematological changes we could find no signs of systemic lupus erythematosus in this patient. An electrophoretic determination of his serum proteins revealed a gamma globulin level of 1·2 g. %, which is relatively high for an infant 3 months of age. Otherwise the serum proteins were normal. He was group 0 Fy(a−) K− S− Le(a+) Rh+ (R_1r), his mother A_1 Fy(a−) K− S+ Le(a−) Rh+. No antibodies against the infant's red blood cells could be demonstrated in the mother's serum, and no platelet antibodies could be detected in either the mother's or the infant's serum (Dr. J. Lundevall). Technical facilities for studying leucocyte antibodies or foetomaternal leucocyte incompatibility were not available.

Discussion

In short, the case history reported was as follows: a woman, 29 years of age, became ill with subacute systemic lupus erythematosus during her fourth pregnancy. At the time of delivery an exacerbation of the disease occurred with haemolytic anaemia, positive Coombs test, leucopenia and possible thrombocytopenia. Her newborn infant developed similar haematologic manifestations, which, however, disappeared at 3½ months of age following treatment with blood transfusions and prednisone.

Pregnancy may be a serious complication to systemic lupus erythematosus, especially in the acute cases, with high maternal and foetal mortality. Ellis and Bereston (1952) collected a series of 69 cases from the United States, 56 with acute and 13 with subacute systemic lupus erythematosus. Treatment with corticosteroids had not been introduced at the time these patients were seen. Among the 56 acute cases 14 deaths were recorded in connexion with the pregnancy, and in addition 11 patients became worse. In the offspring there were 10 deaths *in utero* and six in the neonatal period. Among the 13 women with the subacute form of the disease there were no deaths in connexion with pregnancy or delivery, and a few of them even showed some improvement. In six the pregnancy terminated with abortion, while the other seven gave birth to living, apparently healthy infants. In chronic discoid lupus erythematosus, pregnancy does not seem to involve special hazards for mother or child.

Our knowledge about the causes of foetal or neonatal death as a result of maternal systemic lupus erythematosus is scanty. Hogg (1957) has described the necropsy findings in an infant who died on the second day of life, and who seemed to have signs of congenital systemic lupus erythematosus with typical vascular lesions. This child also had subendocardial fibroelastosis. Based on this observation Hogg advanced the hypothesis that subendocardial fibroelastosis may in some cases be due to a collagen disease. Other cases of congenital forms of the disease have not been reported. But Bridge and Foley (1954), and later other authors (Berlyne, Short and Vickers, 1957; Mijer and Olsen, 1958), were able to demonstrate placental transmission of the L.E. factor to the newborn infant. The L.E. test in these cases remained positive in the infant's blood until about 7 weeks of age, and then became negative. It is not surprising that this factor, being a gamma globulin, can pass the placental barrier.

Haematological manifestations in a newborn infant as a result of maternal systemic lupus erythematosus have not been previously reported. However, this may be partly due to the fact that they have not always been adequately searched for. We do not know precisely when our patient developed his pancytopenia. He looked pale even at birth. His paleness gradually increased, but his blood picture was not studied until he was 2 months old. A severe haemolytic anaemia and a marked leucopenia were then discovered. Blood platelets were not counted at that time. On admission to our department, when he was almost 12 weeks old, increased haemolysis could still be demonstrated. The leucopenia, however, was no longer present. A moderate thrombocytopenia with 114,000 blood platelets per c.mm. was found.

The fact that the patient has remained healthy and kept a normal blood picture since the age of 3½ months strongly supports the concept that his haematologic changes were caused by antibodies transferred from the mother. One must suppose (1) that the pancytopenia of this young woman with systemic lupus erythematosus was due to circulating antibodies, and (2) that there was placental transmission to the infant of these antibodies affecting erythrocytes, leucocytes and thrombocytes.

A similar mechanism is known to operate in chronic idiopathic thrombocytopenic purpura. About 60% of infants born of mothers with this disease get a transient thrombocytopenia, lasting for

about two to four months after birth (Epstein, Lozner, Cobbey and Davidson, 1950; Nelson, 1954) and caused by placental transmission of maternal platelet antibodies.

Passage of red cell antibodies across the placental barrier is of course seen in erythroblastosis foetalis. In this disease, too, the haemolytic process may last for about three months. The occurrence of transient haemolytic anaemia in an infant born of a mother with autoimmune haemolytic anaemia, as in our case, has hitherto not been unequivocally demonstrated (Dacie, 1954; Söderhjelm, 1959), but might perhaps have been present in the case reported by Söderhjelm.

Transient leucopenia (granulocytopenia) in the neonatal period has been described in two siblings (Slobody, Abramson and Loizeaux, 1950; Lehndorff, 1951; Luhby and Slobody, 1956), but must be rare. The two siblings reported by Slobody and coworkers showed a marked granulocytopenia on the third day of life, with complete restitution in three to four weeks. The mother's blood picture was normal; leucocyte antibodies could not be demonstrated. Still, these authors advance the theory that the granulocytopenia might have been elicited by foetomaternal leucocyte incompatibility through a mechanism similar to that of the anaemia in haemolytic disease of the newborn. Payne and Rolfs (1958) have shown that multiparous women have a higher incidence of leucocyte antibodies in their serum than do those who have not been pregnant, a finding which may be due to foetomaternal leucocyte incompatibility. However, they report that so far not a single case of consequent neonatal leucopenia has been found. Simultaneous occurrence of leucopenia in a mother and her newborn infant has been reported in two families by Stefanini, Mele and Skinner (1958). In these cases the mothers were suffering from chronic neutropenia. The infants' blood picture became normal in three to four weeks after birth. In one case leucocyte antibodies could be demonstrated in both the mother's and her newborn infant's serum.

It has been assumed (Dausset, 1956) that the leucopenia in systemic lupus erythematosus may be caused by the presence of the L.E. factor which, as mentioned above, may pass the placental barrier. However, in newborn infants with a positive L.E. test hitherto reported in the literature, leucopenia has not been demonstrated. One cannot be certain whether it has not been present, or whether it has been overlooked.

Summary

A woman of 29, developed signs of subacut systemic lupus erythematosus during her fourt pregnancy. In connexion with delivery an exacer bation of the disease occurred with pronounce haemolytic anaemia, a positive Coombs test, leuco penia, and a mild thrombocytopenia. Her newbor infant also developed a severe haemolytic anaemia leucopenia and thrombocytopenia, but with com plete restitution at 3½ months of age followin treatment with blood transfusions and prednisone.

Placental transmission of the L.E. factor has bee observed by several authors. A single case inter preted as congenital systemic lupus erythematosus has also been reported. But pancytopenia in a newborn infant caused by systemic lupus erythematosus in the mother does not seem to have been described before. The infant's haematological manifestations may be due to the passage of maternal antibodies against the formed elements across the placental barrier.

Infants born of mothers suffering from this should have their blood picture checked during the first months of life, particularly if the mother shows prominent haematological changes.

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PANCYTOPENIA WITH CONGENITAL DEFECTS (FANCONI'S ANAEMIA)

BY

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(RECEIVED FOR PUBLICATION OCTOBER 12, 1959)

Fanconi (1927) drew attention to a syndrome of pancytopenia associated with congenital defects which has since become known as Fanconi's anaemia. Reports of other cases followed from different parts of the world, including one from South Africa (Kessel and Cohen, 1953), but the condition remains a rare one.

We report here five cases of pancytopenia with accompanying congenital anomalies, seen in Cape Town. Some unusual features are mentioned and it will be shown that the syndrome may not be recognized when the associated defects are inconspicuous.

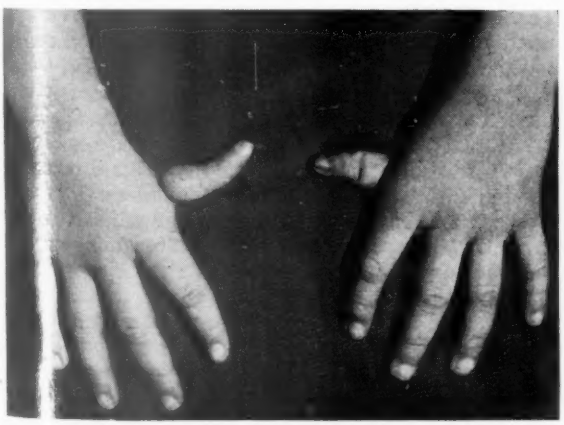
Case Reports

Case 1. D.G., a white boy, was first admitted to Groote Schuur Hospital in January, 1951, at the age of 6 years.

From the age of 14 months he had had recurrent attacks of bronchitis. He had also undergone tonsillectomy, right inguinal herniotomy and dilatation for anal stenosis. For three months before admission he had been pale, anorexic and irritable.

His parents were in good health. Their first child, a girl, was said to have had unilateral polydactyly on the radial side, persistent patency of the ductus arteriosus and subacute bacterial endocarditis and had died at the age of 6 years.

During the patient's 20 admissions to hospital the following features were recorded: he was pale and underweight for his age, weighing 33 lb. at 6 years, and was judged to be of normal intelligence. Microcephaly—head circumference was 19¾ in. at 8 years; microphthalmia, absent testes and hyperpigmentation of the skin were noted. Both thumbs were grossly deformed (Fig. 1) and attached to his hands by soft tissue only. Radiographs showed maldevelopment of the metacarpals and phalanges of the thumbs and retarded ossification of the carpal bones (Fig. 2). The radial pulse was not palpable at either wrist, but the pulsation of the ulnar arteries was forceful. Femoral artery pulsation was normal. A systolic murmur, maximal in the pulmonary area, was heard at each admission. A systolic thrill in the second and third left interspaces and in the neck was occasionally recorded, but radiographs of the chest, screen examination of the heart and electrocardiogram were thought to be within normal limits.



FIGS. 1 and 2.—D.G., aged 7 years. Note abnormality of thumbs and delayed ossification of carpal bones.

The original blood findings were as follows: Haemoglobin was 7·3 g.%; the peripheral blood smear showed anisocytosis and poikilocytosis of the red cells; white cells numbered 12,250/c.mm., of which 80% were lymphocytes, 18% neutrophils, 1% monocytes and 1% eosinophils; his blood group was A Rh positive and his E.S.R. 34 mm. (Westergren) in the first hour. Bone marrow in January, 1953 was normal and a platelet count at the same time was 142,000/c.mm. Reticulocyte counts varied between 0·5 and 5%.

The anaemia was unresponsive to haematinics and was uninfluenced by splenectomy, which was performed in April, 1953. Blood transfusions became necessary at increasingly short intervals. In June, 1955 he was admitted for blood transfusion and shortly afterwards developed pneumococcal meningitis from which he died. The occurrence of petechial cutaneous haemorrhages is first recorded at this time, when a platelet count was 3,000/c.mm. No autopsy was performed.

Case 2. R.W., a white girl, was first admitted to Groote Schuur Hospital in July, 1953 at the age of 6 years.

It was not made known to us at the time that a supernumerary thumb had been amputated when she was 18 months old. Since the age of 3 her parents had noticed that she bruised very easily and she had had recurrent respiratory infections, each temporarily responsive to sulphadiazine, of which her father, a farmer, kept a stock primarily intended for veterinary use. Increasing pallor, fatigue and weight loss had been noticed for two months.

Both her parents and three younger siblings were reported to be well, although it was recalled that her mother had been anaemic in her youth.

On examination the child was judged to be of normal intelligence. She was pale and thin, weighing 40 lb. and petechial haemorrhages were noted in skin, mucous membrane of pharynx and ocular fundi. The Hess test for capillary fragility was positive. A soft systolic murmur, maximal at the cardiac apex, was constantly heard throughout her subsequent admissions. A mid-diastolic murmur, described as blowing in character, was recorded at her first admission and again six months later, but on no other occasion.

The peripheral blood showed a haemoglobin of 4·5 g.%. The smear showed anisocytosis and poikilocytosis of the red cells, and the white cells were 1,360/c.mm. (lymphocytes 78%, neutrophils 16%, staff cells 4%, monocytes 1% and eosinophils 1%). The platelet count was 8,000/c.mm., reticulocyte count 1·8%, E.S.R. 95 mm. (Westergren) in the first hour and the blood group A Rh positive. The bone marrow, frequently examined, was thought on one occasion to show megaloblastic hyperplasia, but on all other occasions, apart from the constant observation that platelets were scanty and megakaryocytes absent, it was thought to be normal. Radiographs of chest, pelvis and long bones, screen examination of the heart, electrocardiogram, blood Wasserman reaction, osmotic fragility of red cells, serum bilirubin, direct Coombs test, Paul-Bunnell test, liver function tests, plasma proteins, fractional test meal and intravenous pyelogram all resulted in normal findings.

A diagnosis of anaemia, neutropenia and thrombocytopenia, possibly due to sulphonamide toxicity, was made and during 14 subsequent admissions there was no reason to alter it. In retrospect, however, it should be mentioned that tendon reflexes were noted to be brisk on more than one occasion, that generalized hyperpigmentation of the skin was noticed at her 12th admission, and that pyuria was a frequent finding, suggesting that there might have been some slight renal anomaly not demonstrated by intravenous pyelography.

The majority of her admissions were on account of gross anaemia with which epistaxis and infections were often associated. Neutropenia and thrombocytopenia were constant findings. Prolonged courses of A.C.T.H., cortisone, prednisone, vitamin B_{12}, folic acid and iron were without benefit, as was splenectomy, performed at her seventh admission in October, 1954. Blood transfusion and antibiotics were the only effective forms of treatment, and, at the last, even these failed. She died of staphylococcal pyaemia with widespread haemorrhagic manifestations, pneumonia and jaundice in August, 1957. No autopsy was performed.

Case 3. Ju.W., younger sister of R.W., was admitted in May, 1959, at the age of 11 years.

For the preceding year increasing pallor and a tendency to bruise easily had been noted by her parents. Six weeks before coming under our care she had been admitted to hospital near her home with a sudden onset of fever accompanied by flitting pains in the knees and ankles. The fever and joint pains were short lived, but her anaemia proved unresponsive to oral and intramuscular iron and to vitamin B_{12} and she was transferred to Cape Town for further investigation.

Her parents and three younger brothers were reported to be in good health.

On examination she was a well grown and intelligent girl weighing 74 lb. Pallor of mucous membranes, a rather darkly pigmented skin and a short, soft systolic murmur, which was loudest at the lower left sternal border, were the only abnormal physical findings detected.

The haemoglobin was 7·5 g.%; the smear showed marked anisocytosis and poikilocytosis of the red cells; the white cells numbered 7,000/c.mm., of which 94% were lymphocytes and 6% neutrophils. Platelets were scanty, the platelet count being 58,000/c.mm. E.S.R. was 36 mm. (Westergren) in the first hour and her blood group A Rh positive. Two attempts at bone marrow aspiration having failed to produce more than a few marrow cells, a bone biopsy was obtained by trephine from the iliac crest. This specimen was pale, with scanty marrow cells, which appeared to be normal and to be present in normal proportions. Radiographs of chest and long bones and an electrocardiogram showed no abnormality. Blood culture was sterile, the Mantoux test negative and the urine normal.

Folic acid 10 mg. twice daily was given for 10 days without benefit. Two pints of blood were transfused and she was sent home.

FIG. 3.—Jo.W., aged 7 years. Note abnormal thumbs; Ju.W. aged 11 years, note difference in size of thenar eminences.

It was felt that the occurrence of hypoplastic anaemia, neutropenia and thrombocytopenia in the two sisters must have either a genetic or an environmental cause. Moreover it was suggested by their father in a letter to us that his three sons were beginning to look pale. Their private doctor kindly sent oxalated specimens of blood and examination of these revealed that one, that of Jo.W. (Case 4), was frankly abnormal. In order to search for any possible environmental influence, one of us (B.G.) arranged to visit the farm, 200 miles away, where the family lived in a region of hot springs. The findings were as follows: (1) Scrutiny of the environment with a Geiger counter failed to reveal any source of excessive ionizing radiation. (2) Investigation, including chemical analyisis of the farm water, failed to reveal any source of chemical poisoning. (3) Jo.W. was found to have abnormal thumbs incapable of active abduction, adduction or extension and Ju.W. was re-examined and found to have a right thenar eminence smaller than her left and to be incapable of abducting or extending the right thumb. (Fig. 3). (4) It was now learnt that mother and father were distantly related and that R.W. had had a supernumerary thumb amputated at an early age.

A diagnosis of Fanconi's anaemia could now be made and Ju.W. and Jo.W. were asked to return to us for further investigation.

J .W. (Case 3) was readmitted in July, 1959. Her haemoglobin, which was 12 g.% on her discharge six weeks previously, had dropped to 7·5 g.%. The cutaneous hyperpigmentation, noted at her first admission, was confirmed by several observers and became more pronounced when her anaemia was again corrected by blood transfusion. There were numerous bruises on her arms and legs and her knee and ankle jerks were very brisk. The significance of slight gynaecomastia was felt to be uncertain in view of her age. Radiographs of her hands showed that the metacarpal and proximal phalanx of her right thumb was of equal length but more slender than that of her left thumb. Intravenous pyelography showed no abnormality.

Case 4. Jo.W., aged 7 years, brother to R.W. and Ju.W., was admitted in July, 1959.

Slight pallor and a tendency to bruise readily had been observed for about three months.

On examination there was the striking abnormality of both thumbs already mentioned. He weighed 44 lb. and his intelligence was thought to be normal. Slight hyperpigmentation was confined to the skin of the axillae. There was some bruising on the legs and arms. Radial pulses were not palpable at either wrist, but the ulnar pulsation was forceful. A short, soft systolic murmur, maximal at the apex, was heard but there was no other evidence of heart disease. The tendon reflexes in the legs were accentuated.

The haemoglobin was 10 g.%; the red cells showed anisocytosis and poikilocytosis; white cells numbered 4,000/c.mm., of which lymphocytes comprised 98% and neutrophils 2%. His blood group was AB Rh positive and the E.S.R. was 35 mm. (Westergren) in the first hour. Very few platelets were seen on the peripheral blood smear, the count being 49,000/c.mm. Three attempts at bone marrow aspiration from different sites produced only scanty marrow cells and further measures to obtain a specimen of marrow were not thought justifiable. Radiographs showed spina bifida of the 6th cervical and 3rd thoracic vertebrae in addition to maldevelopment of the metacarpals. Intravenous pyelography was normal.

Case 5. P.v.d.W., a white boy, first came under our care in January, 1957, when he was 6 years old.

At the age of 18 months he had had a bifid uvula repaired. Apart from chicken pox he had been well until the age of 4 years when excessive bruising and frequent epistaxes commenced. Fatigue and dyspnoea had been noticed for one week prior to admission. His parents and six siblings were said to be healthy.

He was a fair haired boy of average intelligence weighing 41 lb. Numerous bruises were noted, although the Hess test for capillary fragility was negative. His skin was rough and dry and his finger and toe nails were dystrophic. Bilateral epiphora was present due to blockage of both lacrimal ducts. This was improved by probing, but soon recurred and resisted further treatment. A soft, systolic murmur, present at each subsequent admission, was heard at the cardiac apex and lower left sternal border.

His haemoglobin was 5·5 g.%, the red cells showed anisocytosis, poikilocytosis and some polychromasia and the white cells were 4,500/c.mm. Lymphocytes numbered 72%, neutrophils 14%, staff cells 2%, monocytes 7% and eosinophils 5%. Platelets were very scanty, there being only 10,000/c.mm. His blood group was A Rh positive and the E.S.R. 70 mm. (Westergren) in the first hour. Other investigations were: reticulocyte count 4%; bleeding time eight minutes; coagulation time (Lee and White) seven minutes; prothrombin index 100%; thromboplastin generation test abnormal in a manner consistent with thrombocytopenia and clot retraction normal.

The following additional tests resulted in normal findings: Paul-Bunnell, Widal and brucella agglutination tests, blood Wassermann reaction, blood culture, serum bilirubin, direct Coombs test, osmotic fragility of red cells, plasma proteins and radiograph of chest. Mantoux testing was negative and the urine normal.

Radiographs of long bones showed some widening of the medullary cavities consistent with marrow hyperplasia, which was a constant finding in this case. The bone marrow showed normal erythropoiesis and granulopoiesis apart from some normoblasts suggestive of iron deficiency; platelets were scanty and megakaryocytes were not seen.

Ferrous sulphate 180 mg. was given three times daily and the haemoglobin level rose in three weeks to 10 g.%, reticulocyte counts remained high and platelet counts low. He was discharged on oral iron and was seen again three months later for review when the findings were unchanged except that the reticulocyte count had fallen to a normal level and iron deficiency normoblasts had disappeared from the bone marrow.

Nine months later he was readmitted with gross anaemia. Immediate blood transfusion raised the haemoglobin level to 11·5 g.% and prednisone 5 mg. four times daily was then commenced and given for five weeks. This had no effect on the persistently low platelet count, but it was thought possible that a haemolytic aspect of the disease might have been inhibited because, while prednisone was being administered, the haemoglobin level rose steadily to 12·5 g.%. He was discharged again to his home in the country but within a month he was readmitted with extreme pallor. On this occasion he was not transfused. Prednisone was again commenced and after one week oral iron and ascorbic acid were added. Despite the fact that reticulocyte counts remained slightly above normal and the bone marrow continued to show active erythropoiesis, three weeks of this treatment resulted in no rise of haemoglobin. Splenectomy was now performed and one week post-operatively the platelets numbered 332,000/c.mm.

He now remained well for four months, but then again began to complain of dyspnoea and fatigue on exertion. He was readmitted in February, 1959, grossly anaemic and it was found that thrombocytopenia had recurred. Following blood transfusion, prednisone and iron therapy were again tried but without benefit and he was thereafter readmitted for blood transfusion at intervals of approximately six weeks, neutropenia and thrombocytopenia remaining constant findings. On his final admission to hospital he was bleeding into his gastrointestinal and renal tracts as well as into the skin. Blood transfusion failed to control the bleeding and he died on August 22, 1959.

Discussion and Review of the Literature

The disease may be familial, as in Fanconi's original cases, and is then thought to be inherited as a recessive trait (Reinhold, Neumark, Lightwood and Carter, 1952). It may occur sporadically, for which a gene mutation is believed to be the explanation (Dawson, 1955). We have been able to find full descriptions in the literature of 30 cases occurring in 16 families and of 13 cases occurring sporadically.

The Congenital Abnormalities. A list of the congenital abnormalities more commonly associated with the syndrome is set out in the Table. This includes our own cases and is an amplification of a similar one drawn up by Dawson (1955). Hyperpigmentation of the skin, the commonest abnormality, was found in four of our patients. Deformities of thumbs, and sometimes also of the radii, were frequent findings; the former anomaly

TABLE
CHIEF CONGENITAL DEFECTS IN 43 CASES OF THE FULL SYNDROME

Abnormality	Cases
Pigmentation	36
Abnormalities of thumbs	23
Shortness	22
Microcephaly	19
Hypogonadism	15
Hyperreflexia	13
Renal abnormalities	13
Microphthalmia	9
Mental retardation	9
Squint	9
Delayed ossification centres	7
Ear abnormalities	7
Heart abnormalities	6

was present in four of our cases. Several authors commented on delay in the appearance of the ossification centres in the carpal bones; this anomaly was found only in our first case. Shortness of stature, hypogonadism and abnormalities of the nervous system, including mental retardation and hyperreflexia, were not infrequently reported as were renal anomalies. The last took the form of a single kidney (Kunz, 1952; Levy, 1952; Reinhold *et al.*, 1952; Kessell and Cohen, 1953; Cowdell, Phizackerley and Pyke, 1955; Dawson, 1955); ectopic position of one kidney (Beautyman, 1951; Francis, Moir and Swift, 1955) and, in one case, a horse-shoe kidney (Dacie and Gilpin, 1944). Congenital cardiac anomalies were occasionally found. All our cases had systolic murmurs, which persisted after transfusion, but further cardiological investigation was not suggestive of any specific abnormality. We are not sure, therefore, whether the murmurs were indicative of some minor cardiac pathology or not. One of our children had a partial spina bifida of a cervical and a thoracic vertebra. This occurred in one of Shaw and Oliver's cases (1959), while Lynch, Sherman and Elliott (1954) stated that they had heard of a child with pancytopenia and this associated anomaly. A feature, found in two of our cases, which we have not seen mentioned elsewhere, was the fact that the radial pulses could not be felt. If Case 5 (P.v.d.W.) is accepted as belonging to the syndrome, his anomalies are yet others to add to the list.

The Blood Picture. In the protocols consulted, all patients had greatly reduced platelet counts and in most cases there was a leucopenia especially affecting the neutrophils. Variation in size, shape and colour of the red cells was common. Reticulocyte counts varied from less than 1% in many cases to quite high levels in others. In cases in which the sedimentation rate was reported this was nearly always considerably raised, but as there was usually an accompanying anaemia the significance of this finding is uncertain. The bone marrow, sometimes initially described as normal, eventually nearly always showed reduced numbers of all blood forming elements.

Age of Onset and Sex Distribution. The more obvious defects are usually noticed soon after birth though some are not apparent until later. Anaemia is not usually manifest until after 6 years of age, although its onset has been reported both earlier and later than this. There are cases on record where the anaemia only became apparent in adult life (Rohr, 1949; McAlpine, 1954; Cowdell *et al.*, 1955). On the other hand, Emery, Gordon, Rendle-Short, Varadi and Warrack (1957) have reported two infants dying in the neonatal period. Both had haemorrhagic manifestations with scanty platelets and in both cases the radii were absent. They quoted five similar cases from the literature. All were sporadic in origin. Shaw and Oliver (1959) have recently given an account of the same blood and skeletal defects in two siblings in the first months of life. These findings indicate that the anaemia may, on occasion, occur in extreme youth in both the sporadic and familial types of Fanconi's anaemia.

In the cases we have studied or read about, 43 in all, the disease occurred twice as often in boys (29) as in girls (14), but as the numbers are small it is not certain if this is the true sex incidence.

Variants. There appear to be possible variants of the syndrome. Estren and Dameshek (1947) described two families in which three and five members respectively died from hypoplastic anaemia. Though none of these had associated anomalies, their familial nature would seem to link them with Fanconi's anaemia.

In another report Cowdell *et al.* (1955) tell of two brothers both of whom had typical congenital defects. One of them showed anaemia at the age of 22 years; the bone marrow was hypoplastic and he died one year later. The other brother developed leukaemia when 27 years of age. This suggests another direction in which the disease may show itself.

Treatment and Prognosis. There is no known curative treatment. All types of haematinics have been tried and steroids have been used in some of the cases reported (Kunz, 1952; Kessell and Cohen, 1953; Francis *et al.*, 1955) as well as by ourselves. No real benefit has resulted from any of these forms of treatment. In a few cases it has been claimed that splenectomy has improved matters, particularly when the reticulocyte count has been high, but for the most part the course of the disease has been uninfluenced. There was no improvement in our three patients who had their spleens removed. Repeated blood transfusion is the only means by which definite temporary improvement can be effected. Intervals between transfusions become progressively short and eventually blood has to be given about every two months and sometimes more frequently.

The disease is invariably fatal, with the single exception of Dawson's (1955) case of a girl first seen with anaemia at 10 years of age. At the age of 20 she was reported to be alive, well and married. The usual duration of illness is from a few months

to several years, the average life expectancy being two to four years after the first appearance of anaemic symptoms. In most cases death has been due to infection or massive haemorrhage.

Fanconi's anaemia should be considered in the differential diagnosis of all cases of pancytopenia. A careful examination for congenital defects, however minor, should be made and other members of the family should be investigated for signs of the trait. If this is not done the syndrome may not be recognized, as occurred in the first two members of the family we have described. It was only when the third child was seen that the correct diagnosis was made and the significance of barely noted defects in his sisters was appreciated.

Summary

Four cases of Fanconi's anaemia are presented as well as a fifth case which it is suggested may be another example of this condition.

That the disease may not be recognized if the associated congenital defects are minor ones is exemplified in two out of three cases found in one family.

The literature is reviewed and the congenital defects which commonly occur are listed and discussed including some unusual manifestations in our cases.

Our thanks are due to Professor F. J. Ford for helpful advice, to the Medical Superintendent, Groote Schuur Hospital for permission to publish and to Mr. B. Todt, hospital photographer, for the photographs.

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Addendum

When this article was submitted the paper by Shahidi and Diamond (1959) on the treatment of aplastic anaemia with a combination of testosterone and steroids had not yet appeared.

Our two surviving children are now being treated in this way and the results will form the subject of a future communication.

STUDIES IN HIRSCHSPRUNG'S DISEASE

BY

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(RECEIVED FOR PUBLICATION NOVEMBER 12, 1959)

The morbid anatomy of Hirschsprung's disease is now firmly established. Swenson and Bill (1948) noted that the dilated colon which figures so largely in the earlier description of the disease terminated at a point proximal to the anus and was followed by a spastic segment. They concluded that the obstruction was due in some way to this segment and that the hypertrophy and dilatation of the bowel above was secondary to this obstruction.

Further work by Zuelzer and Wilson (1948), Bodian, Stephens and Ward (1949), Whitehouse and Kernohan (1948) and Swenson, Rheinlander and Diamond (1949) has shown that in the narrowed spastic segment there is a complete absence of the ganglion cells which form Meissner's and Auerbach's intramural plexuses. Instead there are large bundles of non-medullated nerve fibres occupying the position of the plexuses. This aganglionic segment extends from the anus up to the dilated part of the bowel. Examination of the dilated colon itself shows that there is hypertrophy of the muscle walls, but that the intramural ganglion cells are present in the normal quantities and arranged in the normal manner.

The abnormalities of function of this aganglionic segment are less clearly defined. Barium enema shows that this segment extends from the anus to the rectosigmoid junction or distal sigmoid colon; it appears narrow and can sometimes be seen to undergo segmentation. Proximal to this segment the bowel enlarges to form the typical megacolon. Using a technique which involves the recording of intracolonic pressures by means of multiple balloon at various levels in the lower bowel, Swenson *et al.* (1949) showed that there was increased tone with an absence of normal peristalsis in the narrowed segment. Davidson, Sleisenger, Steinberg and Almy (1955) described the effect of mecholyl on the activity of the colon in Hirschsprung's disease as recorded by catheters in the lumen of the gut. They noted that in records taken from the aganglionic segment of six patients with Hirschsprung's disease, mecholyl produced no change; whereas in 20 normal subjects there was no change in 11, and relaxation of the bowel in nine. In discussing their results they noted the possibility of using this method for mapping out the aganglionic segment of intestine, and they also commented on the absence of any increased sensitivity of the intestine to cholinergic drugs, such as is found in the aganglionic part of the oesophagus in achalasia of the cardia, and such as would be expected from Cannon's law of denervated structures. They conclude that this is due to the lesion being congenital rather than acquired.

It seemed that there was room for further investigation of the changes in the colon which occurred in Hirschsprung's disease. In the experiments which are described below, various properties of intestinal muscle obtained at operation from the aganglionic segment of gut from patients with Hirschsprung's disease and from a similar region in normal controls were examined to determine more accurately the nature of the derangement of function.

The following investigations were carried out:

(1) The response of the muscle strips to the action of various drugs *in vitro*;

(2) The response of muscle strips *in vitro* to electrical stimulation at various voltages and duration of stimulation;

(3) The presence or absence of ganglion cells in all specimens examined by the above methods was checked by ordinary histological means.

Response to Drug Stimulation

Method. Specimens of muscle both longitudinal and transverse were removed at operation from the aganglionic segment of bowel of patients with Hirschsprung's disease and from similar regions of the pelvi-rectal junction and upper rectum from patients with miscellaneous conditions. The mucous membrane was removed and strips of muscle were suspended in oxygenated tyrode at 37° C. The contractions of the muscle were recorded by a lever writing on a smoked drum.

Results. The response of the muscle strips to stimulation by drugs and the effect of various

blocking agents is shown in Tables 1, 2 and 3.

It can be seen that the normal muscle, and the muscle from both the aganglionic segments can all be stimulated by acetylcholine and that this response can be blocked by atropine but not by succinyl choline. Furthermore, muscles from all three sites will respond to nicotine with a contraction, although sometimes this response could only be obtained after the addition of eserine. It was also found that eserine would always increase the amplitude of the contraction with nicotine. The nicotine induced contraction could always be partially or completely blocked by hexamethonium and completely blocked by atropine. These findings hold true for both longitudinal and transverse muscle strips.

TABLE 1
THE RESPONSE OF LONGITUDINAL AND TRANSVERSE NORMAL MUSCLE FROM THE UPPER RECTUM AND COLON TO DRUGS

Stimulating Agent	Response	Blocking Agent		
		Hexamethonium (2·0 mg.)	Atropine (100 μg.)	Succinyl Choline (2·0 mg.)
Nicotine 400 μg.	+ (2) 0 (1)	B1	B1	0
Eserine 100 μg. + Nicotine 400 μg.	+ Increased response	B1	B1	0
Acetylcholine 20-50 μg.	+		B1	0
Noradrenaline 100 μg.	0 or fall in base line			
Adrenaline 100 μg.	0 or fall in base line			

50 ml. bath; + = contraction; B1 = block; 0 = no effect
Figures in brackets = number of experiments

TABLE 2
THE RESPONSE OF TRANSVERSE MUSCLE FROM THE AGANGLIONIC SEGMENT OF GUT IN HIRSCHSPRUNG'S DISEASE

Stimulating Agent	Response	Blocking Agent		
		Hexamethonium (2·0 mg.)	Atropine (100 μg.)	Succinyl Choline (2·0 mg.)
Nicotine 400 μg.	+ (4) 0 (1)	B1 (2)	B1 (2)	0 (2)
Eserine 100 μg. + Nicotine 400 μg.	+ (5) Increased in all specimens	B1 (3)	B1 (5)	0 (2)
Acetylcholine 20-50 μg.	+ (3)		B1 (3)	0 (2)
Noradrenaline 100 μg.	0 (1) Base line lowered (3)			
Adrenaline 100 μg.	0 (1) Base line lowered (3)			
5 Hydroxy tryptamine	Base line lowered (1)			

As for Table 1

TABLE 3
THE RESPONSE OF LONGITUDINAL MUSCLE FROM THE AGANGLIONIC SEGMENT OF GUT IN HIRSCHSPRUNG'S DISEASE

Stimulating Agent	Response	Blocking Agent		
		Hexamethonium (2·0 mg.)	Atropine (100 μg.)	Succinyl Choline (2·0 mg.)
Nicotine 400 μg.	+ (4) 0 (2)	B1 (1)	B1 (2)	0 (2)
Eserine 100 μg. + Nicotine 400 μg.	+ (4) Increased in all specimens	B1 (3)	B1 (2)	0 (2)
Acetylcholine 20-50 μg.	+ (3)		B1 (3)	0 (2)
Noradrenaline 100 μg.	0 (3) Base line lowered (1)			
Adrenaline 100 μg.	0 (2) Base line lowered (1)			
5 Hydroxy tryptamine 100 μg.	0			

As for Table 1

It is widely held that the stimulating action of nicotine is confined to the ganglion cell and that it has no action on either pre- or post-ganglionic nerve fibres or on smooth muscle. In the case of the normal gut, the response is as would be expected, but the contractions of the aganglionic segment from the subjects with Hirschsprung's disease, which could be consistently produced by nicotine, are more difficult to explain. The fact that the nicotine induced contractions could be blocked by atropine and augmented by eserine suggested that the nicotine was stimulating some structure within the colon wall which would release acetyl choline and which was associated with some cholinesterase system.

Response to Electrical Stimulation

In 1955 Paton described a method of stimulating the guinea-pig intestine by means of coaxial electrodes. He concluded that it was possible to distinguish by this method of excitation between pre-ganglionic, post-ganglionic and effector cell structures.

The nature of our specimen obtained at operation made this method of stimulation impossible, but it was considered worthwhile to investigate the nature of their response to electrical stimulation by another method.

Method. The strip of muscle was suspended in oxygenated tyrode at 37° C. Silver electrodes were applied to both ends of the strip and just before stimulation the level of the tyrode was lowered until the muscle and electrodes were completely uncovered. The muscle was then stimulated along its longitudinal axis and the contraction recorded on a revolving smoked drum.

The stimulator provided simple rectangular voltage pulses of variable duration (10 μsec. to 300 msec.) and amplitude (0 to 200 volts). Its output impedance was 300 ohms. In preliminary experiments the current wave form was observed simultaneously with the voltage wave form by means of a double beam cathode ray oscillograph. It was confirmed that the current wave form was also substantially rectangular except for the usual small spike of relatively short duration (associated with the capacitative component of the impedance between the electrode) at the rising edge of the pulse. The resistance of the electrodes and specimen ranged from 2,000 to 4,000 ohms. For example, for a pulse of amplitude 100 volts the current was of the order of 40 mA. With this longitudinal arrangement of the electrodes a considerable proportion of the total current presumably flows along the moist film over the surface of the specimen and does not contribute to the effective stimulus. The threshold voltage required for stimulation was determined by increasing the amplitude of single pulses in steps until a slight muscular contraction was observed. The tyrode level was then raised and the muscle allowed to rest for five minutes before another determination of threshold for a pulse of longer duration; thus intensity duration curves were constructed.

Results. Fig. 1 shows the intensity duration curve obtained from muscle from the upper rectum. It can be seen that the pattern produced with the longitudinal muscle differs a little from that obtained by stimulating transverse muscle, furthermore, after the muscle is atropinized there is a shift in the curve obtained from transverse muscle but not in that obtained from longitudinal muscle.

Fig. 2 shows the curves obtained in transverse muscle from the aganglionic upper rectum of patients with Hirschsprung's disease and it can be seen that all samples show a shift to the right and are similar to those found in atropinized normal muscle. However, the longitudinal muscle from patients with Hirschsprung's disease is similar to that from normals (Fig. 3).

Discussion

These experiments were undertaken to investigate some of the properties of aganglionic intestinal smooth muscle from subjects with Hirschsprung's disease.

The first group of experiments was concerned with the response of this muscle to various drugs. The response of the aganglionic muscle to nicotine was surprising; all the evidence obtained suggested that a structure was being stimulated which was capable of releasing acetylcholine, but extensive search failed to reveal any ganglion cells. It would appear, therefore, that the stimulating effect of nicotine as far as the intestine was concerned extended beyond the ganglion cells and that other structures could also be stimulated. Of the nature of these structures it is only possible to speculate, but the tissues which are most obvious or most likely to be concerned are the whorls of non-medullated nerve fibres which appear in the position usually occupied by Auerbach's plexus and it is not unreasonable to suggest that these structures are capable of being stimulated by nicotine to release acetylcholine.

Experiments by Kottegoda (1953) strongly suggest that nicotine is capable of releasing adrenaline-like substances from isolated rabbit ear and that this action can be blocked by hexamethonium. It seems that release of adrenaline from local chromaffin tissue is unimportant here as noradrenaline relaxes rather than contracts this muscle and the augmentation of the response by eserine and its blocking by atropine suggest a cholinergic rather than an adrenergic mechanism.

The hope of clarifying the situation by differentiating between stimulation of muscle and nerve by varying the durations of electrical pulse wave was disappointing. Small difference could be detected between the transverse muscle from the aganglionic segment on the one hand and normal gut on the other. As far as they went they suggested that it was not possible to stimulate the release of acetylcholine by electrical means as in normal intestine, but the differences were very small and the possibility of some form of artefact could not be excluded.

It can therefore be concluded that in the aganglionic segment of gut in Hirschsprung's disease, although there are no ganglion cells present, there are certainly structures which can release acetylcholine when treated with nicotine and cause the intestine to contract.

The most likely site of this acetylcholine release would be the whorls of tissue which appear to replace Auerbach's plexus in the wall of the gut. Whether these structures are capable of playing any part in intestinal activity is not clear, but the presence of some structure which resembles nervous tissue, and which is capable of releasing acetylcholine, may account for the absence of hypersensitivity of the intestine to cholinergic drugs. For to obey Cannon's law of the hypersensitivity of denervated structures the muscle should be truly denervated.

Summary

The response to drugs and electrical stimulation of strips of aganglionic intestine from patients with Hirschsprung's disease has been determined and compared with normal muscle from the same level.

The results show that there is present in the

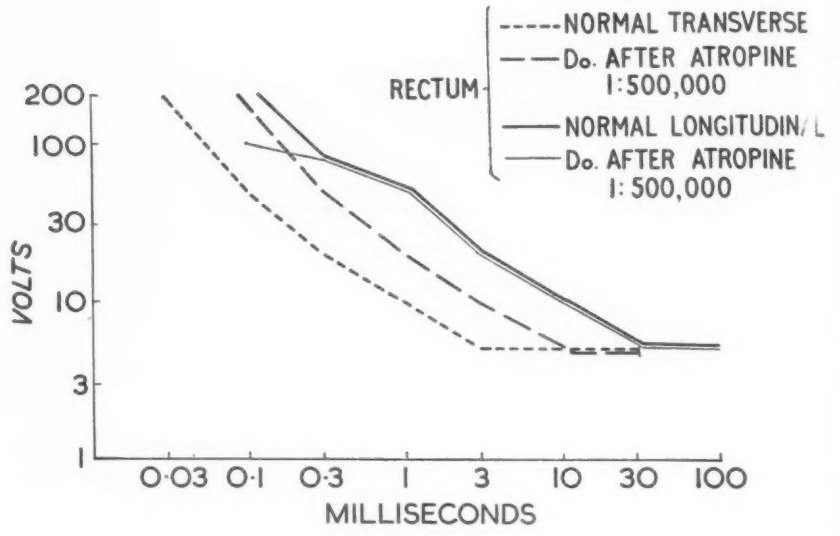

FIG. 1.—Intensity duration curves of normal transverse and longitudinal muscle from the upper rectum before and after atropine 1 : 500,000.

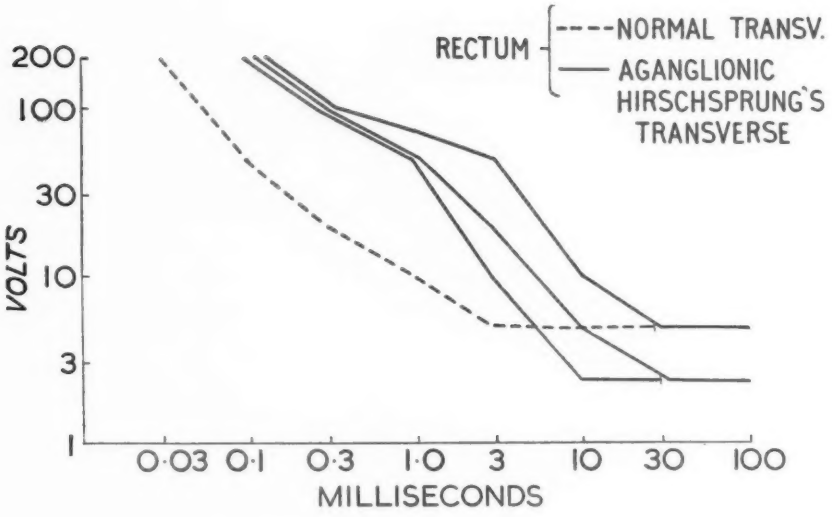

FIG. 2.—Intensity duration curves of transverse aganglionic muscle from the upper rectum of three subjects with Hirschsprung's disease compared with normal muscle.

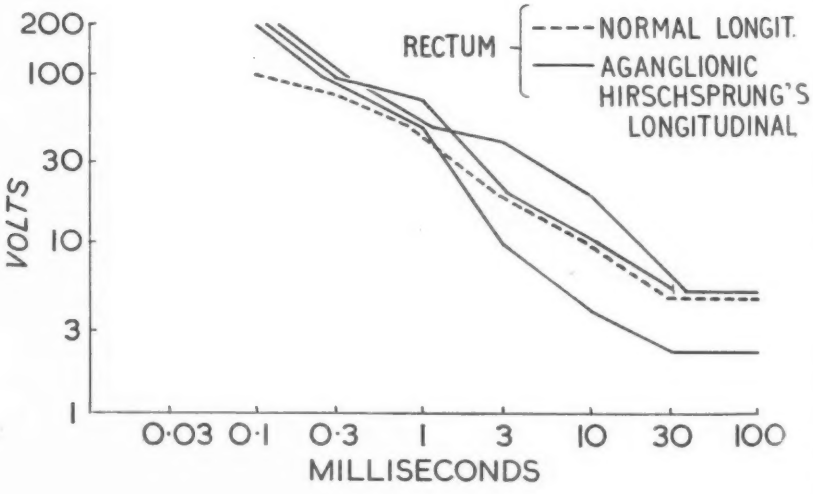

FIG. 3.—Intensity duration curves of longitudinal aganglionic muscle from the upper rectum of three subjects with Hirschsprung's disease compared with a normal.

ganglionic segment some structure, which on timulation with nicotine is capable of initiating contraction mediated by acetylcholine release.

With electrical stimulation, no such acetylcholine release could be demonstrated.

The significance of these results is discussed.

We would like to thank Mr. Grant Massie and Mr. Nixon for their cooperation in providing material removed at operation, and Mr. B. D. Cox for his technical assistance.

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SPONTANEOUS PERFORATION OF THE COLON IN THE NEWBORN INFANT

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(RECEIVED FOR PUBLICATION SEPTEMBER 15, 1959)

If one excludes those cases of perforation which are secondary to volvulus, intestinal atresia, congenital bands, intussusception, herniation of the bowel, meconium ileus or Hirschsprung's disease, there remains a group of newborn infants who develop perforation of the colon without apparent cause.

Spontaneous perforation of the colon in the neonate was first described by Breslau in 1863. It is a rare event and up until 1939 only 26 case reports could be traced in the medical literature by Thelander.

A number of factors have been considered in the aetiology of spontaneous perforation such as trauma during delivery (Zillner, 1884), congenital defects of the bowel with diverticulum formation (Fischer, 1928), localized vascular insufficiency, and intrauterine or post-partum infection (Thelander, 1939). In 1888 Paltauf reported five cases which he attributed to coprostasis. This aetiological concept has recently received support from the clinico-surgical and pathological studies by Zachary (1957) and Emery (1957) of a group of newborn infants in whom inspissated faecal plugs gave rise to stercoral ulceration with perforation. These authors suggest that the observed faecal impaction may be due to an imbalance between fluid absorption and of propulsion of material along the colon. More recently Haas (1958) has reported a newborn infant with perforation of the transverse colon in whom a haemangiomatous abnormality at the site of perforation was demonstrated.

There still remains a group of newborn infants with one or more perforations of the colon and in whom no clear cut cause can be discovered.

In this paper two further cases of spontaneous perforation of the colon are reported. In one of these, perforation occurred during or immediately after birth and this was associated with marked intraperitoneal haemorrhage. The cause of the perforation was undetermined. The other child was a premature infant who developed the perforation nine days after delivery and histological examination showed fungal infection at the site of perforation.

Case Reports

Case 1. This female infant was delivered at term as a vertex presentation by a district midwife after an uneventful pregnancy. The child appeared to be vigorous after birth, but abdominal distension with oedema of the vulva was noted. One blood-stained stool was passed after birth and this led to the admission of the child to this hospital.

On examination, six hours after delivery, the child appeared somewhat pale but not greatly distressed. The weight was 5 lb. 5 oz. and the rectal temperature was 95° F. The most striking feature was marked distension of the abdomen. There were prominent dilated veins on the anterior abdominal wall which was oedematous in its lower half. There was also oedema of the vulva. Percussion of the abdomen elicited shifting dullness. A radiograph of the abdomen showed air in the stomach and small bowel. There were no fluid levels indicating obstruction. Examination of venous blood revealed a haemoglobin level of 9·0 g./100 ml.

An abdominal paracentesis at McBurney's point yielded blood-stained fluid with a haemoglobin level of 2·5 g./100 ml. A preoperative diagnosis of rupture of the liver was made and the child was transfused with 100 ml. of group O Rh positive compatible blood. At laparotomy blood-stained fluid escaped from the peritoneal cavity. Floating in this fluid were fragments of fresh meconium (later confirmed histologically). Careful inspection of small and large bowel failed to reveal a perforation. A Meckel's diverticulum was found, but it appeared to be intact. No rupture of the liver was found. The omentum was stained green by the meconium but there was no evidence of peritonitis.

The abdomen was closed again and the child was maintained on intravenous fluid (0·2% saline in 5% invert sugar) while gastric suction was applied. There was no indication of postoperative bleeding, but

8 hours after the operation she suddenly collapsed and died.

At necropsy the peritoneal cavity contained a small quantity of semi-fluid dark brown material. There was some adherence of the bowel loops. A small perforation 3-4 mm. in diameter was found in the region of the hepatic flexure of the ascending colon and a small quantity of meconium was emerging from the perforation. The anatomical position of the bowel at autopsy appeared normal and there was no evidence of volvulus or intussusception. There was thus no obvious cause for the perforation. Other organs showed no abnormalities except for some patches of atelectasis of the lungs.

Histology of sections of the bowel at the site of perforation revealed merely a break in the continuity of the wall with some necrosis of the wall adjacent to the perforation. Ganglion cells were present in normal numbers. The pancreas showed no obvious lesion. The lungs were congested and oedematous.

Case 2. This male infant was born at this hospital weighing 3 lb. The mother developed puerperal sepsis and the infant at 3 days old was transferred to the premature infant unit, his weight then being 2 lb. 11½ oz. Apart from mild icterus, no abnormalities were detected on clinical examination. He was given feeds of undiluted expressed breast milk from the third day. On the fifth day of life the jaundice had become more intense. The serum bilirubin level was 12 mg./100 ml. Meconium was passed on the fourth and sixth days of life but no stools were noted on the seventh, eighth and ninth days of life. On the ninth day, the infant vomited a feed which was not stained with bile. Some slight distension of the abdomen was noted. A glycerine suppository was prescribed and oral feeding of expressed breast milk was continued. Later in the day two brown watery stools were passed and one of them was blood-stained.

The following day (day 10) the infant continued to vomit and developed gross gaseous distension of the abdomen. The clinical state of hydration was satisfactory. A radiograph of the abdomen revealed the presence of a well-marked pneumoperitoneum (Fig. 1). Gas was present in the small bowel without evidence of fluid levels, and for this reason the site of perforation was thought to be in the colon. Feeds were stopped and intravenous therapy was started with 0·2% saline in 5% invert sugar with the addition of 2·0 g. of potassium chloride to 1,000 ml. of solution. The child was also given 100,000 units of penicillin intramuscularly every eight hours and 50 mg. of streptomycin intramuscularly every 12 hours. On the eleventh day the child's abdomen was still markedly distended and there was oedema of the scrotum. An ill-defined mass could be palpated in the left flank. The infant had also developed oral thrush which was treated with 50,000 units of Nystatin ('mycostatin') every eight hours. On the tenth day the child passed two small scybala. The child's condition continued to deteriorate and death took place on the twelfth day of life.

At necropsy there was marked meconium peritonitis. The peritoneal cavity contained 150 ml. of

FIG 1.—Radiograph of the abdomen showing a large accumulation of air under the diaphragm and in the right scrotal sac.

FIG. 2.—Colon with large perforation in anterior wall immediately distal to splenic flexure.

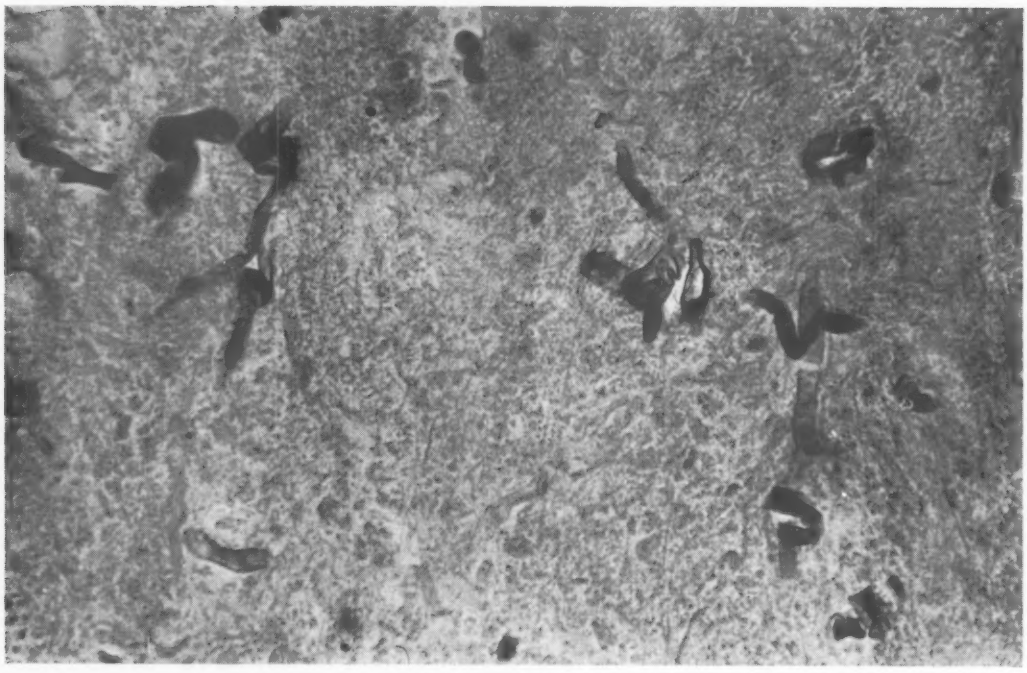

FIG. 3.—Wall of colon adjacent to the perforation showing numerous fungal hyphae.
(Periodic-acid Schiff × 480.)

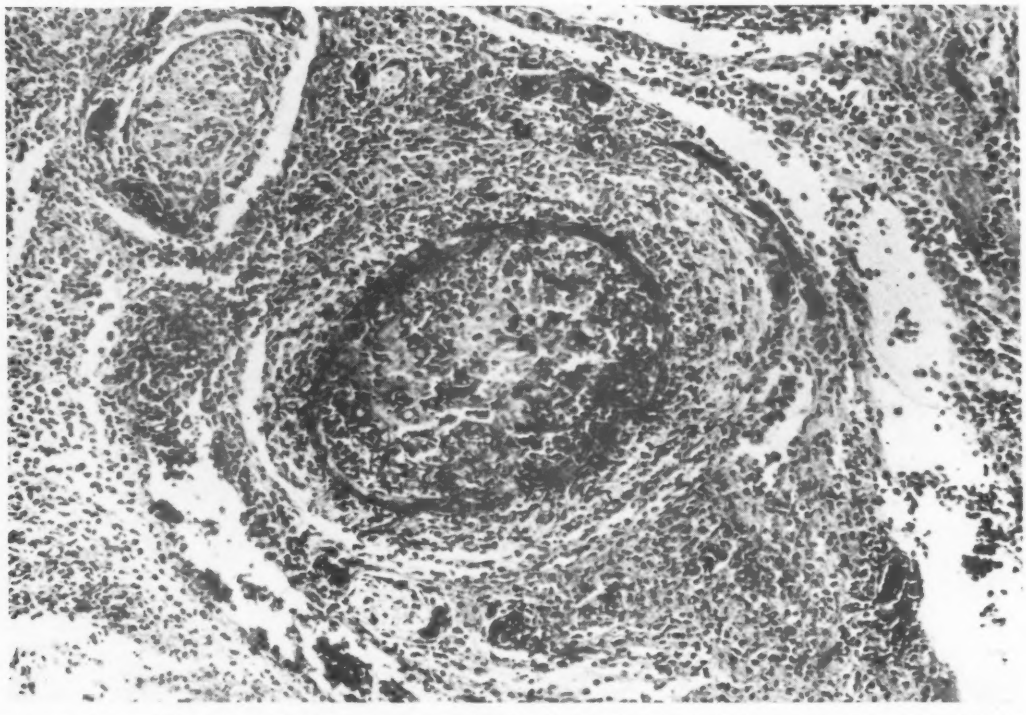

FIG. 4.—Blood vessel in wall of colon adjacent to the perforation showing invasion by inflammatory cells and fungal hyphae.
(Haematoxylin and eosin × 150.)

reen purulent fluid. Loops of bowel were densely adherent to the lateral abdominal wall on the left. A large perforation 0·5 cm. in diameter (Fig. 2) was present about 2·5 cm. below the splenic flexure in the anterior wall of the descending colon.

There were still some yellow flecks of inspissated meconium around the perforation and floating in the peritoneal exudate. Anatomically the bowel was normal, and there was no evidence of a volvulus or an intussusception.

Section of the bowel wall at the site of the perforation showed the surrounding mucosa to be necrotic and haemorrhagic. There was haemorrhage into the submucosa and infiltration of the entire wall by polymorphs. The serosa was acutely inflamed and covered by necrotic debris. Fungal hyphae consistent in appearance with the fungus mucor, or the related rhizopus, were present in the lumen of the bowel, in the wall and in the serosa (Fig. 3). The fungal filaments were large and showed absence of cross-wall formation with free and irregular branching, features suggesting origin from the mucoraceae. In many areas the fungi were invading the walls of blood vessels and had come to lie within their lumens (Fig. 4). Unfortunately cultures of the fungus were not made before the tissues were fixed in formalin.

Histology of the pancreas was normal.

Discussion

Our first case presented the clinical picture of intraperitoneal haemorrhage. Hence a preoperative diagnosis was made of rupture of the liver, which is the commonest solid viscus to be damaged in the newborn infant (Stein and Wright, 1953; Arden, 1951; Brown, 1957).

At operation the surprise finding of meconium in the peritoneal cavity, in addition to the blood, indicated perforation of a hollow viscus. The site of perforation was not detected at laparotomy. This difficulty of locating the site of perforation has been encountered by others, and it happened in four of the cases reported by Thelander (1939). Standard (1952) in reporting his case, which was successfully treated surgically, admits that the perforation would not have been visible but for the presence of leaking barium suspension which he had given to the infant. In a case reported by Franklin and Hosford (1952), the perforation was only found at the second operation.

Necropsy in our first case failed to reveal a cause for the perforation, but it must be admitted that a close study of the blood supply to the affected segment of bowel was not carried out. The clinical and experimental studies of Louw and Barnard (1955) have indicated that vascular occlusion plays an important role in the production of intestinal atresia in the newborn infant. Their work may have some application in the elucidation of the aetiology of spontaneous perforation of the colon. We suggest that, in future, a careful study be made of the blood supply to the area of a spontaneous perforation of the colon. We have assumed that the intraperitoneal bleeding in our case arose from the same site as the perforation, but this was not obvious at autopsy, the bleeding having ceased post-operatively.

Case 2 is of interest in that this premature infant was progressing satisfactorily until the ninth day of life. The child was starting to regain its post-natal weight loss, when it failed to pass stools for three successive days. As in Case 1 there was the passage of one blood-stained stool and it is possible that this finding in the presence of abdominal distension may be of help in the diagnosis of spontaneous perforation of the bowel.

Three possibilities suggest themselves as to the cause of the perforation in Case 2. Firstly this perforation could have followed on stercoral ulceration caused by inspissated meconium. The passage of two small hard pieces of faeces and the finding of residual thickened meconium at necropsy are in favour of this suggestion. However, we were unable to analyse the water content of the meconium as was done by Emery (1957).

Secondly the perforation may be aetiologically connected with the finding of mucor (or rhizopus) in the bowel wall at the site of perforation. Mucor has been found in association with perforation in other parts of the gastro-intestinal tract. Moore, Anderson and Everett (1949) described a widespread ulcerative colitis in a non-diabetic female aged 37 years caused by mucor which resulted in death after perforation and generalized peritonitis. Watson (1957) reported perforation of the stomach in association with mucormycosis in a child of 26 months suffering from malnutrition. A similar perforation was described by Gatling (1959) in a 4-day-old neonate. Thus this fungal infection may have been the primary cause of the perforation in Case 2. It is also possible that the fungus aggravated a perforation caused initially by hardened meconium.

Until recently the prognosis of spontaneous perforation was thought to be uniformly hopeless. However, in 1952, Standard, in America, and Franklin and Hosford, in Britain, reported survivals following surgical repair. Thus laparotomy is probably advisable whenever the condition of the patient permits. Preliminary decompression of the abdomen may be necessary to increase vital capacity (Standard, 1952).

Summary

Two cases of spontaneous perforation of the colon are reported, one in a full term and the other in a premature infant. There was an associated intraperitoneal haemorrhage in Case 1, and in this infant no demonstrable cause was found for the perforation.

In the second baby the perforation was found in association with inspissated meconium and the presence of fungal infection in the bowel wall morphologically either mucor or rhizopus. Unfortunately cultures of the organisms were not taken.

Our thanks are due to Dr. I. Frack, Superintendent, Baragwanath Hospital, for permission to publish these cases, Dr. E. Kahn, Senior Paediatrician, for criticism and advice, the Director of the South African Institute for Medical Research, for facilities granted, and Mr. M. Ulrich for the photographs.

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THE PROGNOSIS IN IDIOPATHIC HYPERCALCAEMIA OF INFANTS

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(RECEIVED FOR PUBLICATION SEPTEMBER 24, 1959)

Two distinct types of idiopathic hypercalcaemia of infants have been recognized; a mild or simple type, in which recovery is said to be complete, and a severe type, which results in death or physical and mental retardation (Lightwood and Stapleton, 1953; Lowe, Henderson, Park and McGreal, 1954). Although most cases conform to one or other type, it has recently become apparent that the distinction is not a clear one, and that cases with features of both types may occur (Russell and Young, 1954; Rhaney and Mitchell, 1956; Joseph and Parrott, 1958). Moreover, a few of the supposedly mild cases have died and autopsy has disclosed nephrocalcinosis, affecting mainly the medulla of the kidney (Rhaney and Mitchell, 1956). Hence it is of some importance to determine whether infants with the simple type who recover clinically sustain any permanent renal damage.

The severe form of idiopathic hypercalcaemia is accompanied by considerable dwarfing (Schlesinger, Butler and Black, 1956; Fellers and Schwartz, 1958), while infants with the simple type show retardation of growth during the acute phase of the illness and often for some time thereafter (Creery and Neill, 1954). It is therefore of interest to know how long this retardation persists after the biochemical disturbance has been corrected.

No full follow-up study has yet been reported although Forfar, Balf, Maxwell and Tompsett (1956) gave some details of four cases followed for one to three years; Creery and Neill (1954) briefly described the progress of their patients up to 18 months after the illness, and there have been reports on single cases (Bonham Carter, Dent, Fowler and Harper, 1955; Smith, Blizzard and Harrison, 1959). With a view to obtaining more detailed information about the prognosis, the progress of all children with the simple type of idiopathic hypercalcaemia seen in Dundee during a period of four years has been followed.

Details of the follow-up study

From 1953 to 1956 inclusive, 18 infants were diagnosed as having the simple type of idiopathic hypercalcaemia. The principal clinical features of the group have been briefly reviewed elsewhere (Mitchell, 1958) and detailed case histories have been recorded for eight of the infants; Cases 2, 3, 4 and 6 by Lowe *et al.* (1954); Cases 1 and 2 by Morgan, Mitchell, Stowers and Thomson (1956); and Cases 1 and 3 by Rhaney and Mitchell (1956). In Dundee the criterion now accepted for the diagnosis of hypercalcaemia in infants is a level of plasma calcium above 12·0 mg. per 100 ml. measured on two separate occasions, using an oxalate-permanganate method for the determination of calcium. During the four-year period, at least five other infants were believed to have idiopathic hypercalcaemia of the simple type (two were included in the report by Lowe and his colleagues in 1954 as Cases 5 and 7), but the above criterion was not fulfilled and they are not included in the group. Of the 18 infants in whom the diagnosis was regarded as established, four died and three of these were studied at necropsy (Rhaney and Mitchell, 1956). The 14 survivors are the subject of this report.

Tests of renal function were carried out on all children who had shown any evidence of possible renal involvement during the original illness, i.e. all those whose urine contained leucocytes at any time during the illness or who had had a level of blood urea over 50 mg. per 100 ml. on any occasion. The tests were made at least once between two and five years after the onset of symptoms.

Since the children had endured much investigation and treatment in the past, and most were in the pre-school age group when clinical investigation is most difficult, it was considered desirable to limit the study to the minimum required to provide a reasonable estimate of kidney function. Thus tubular function was assessed by the ability to concentrate and acidify the urine and glomerular function by the clearance of creatinine. Since the determination of creatinine clearance by methods which also measure non-creatinine chromogen is not satisfactory (Doxiadis and Goldfinch, 1952; Barnett and

Vesterdal, 1953), specific endogenous creatinine was measured by Hare's method (1950) using a Unicam SP600 spectrophotometer. Two timed collection periods of between one and two hours were used and the results were expressed in terms of surface area calculated from the Dubois nomogram. Urea clearance was also estimated but in most cases the rate of urine secretion was not adequate for maximum clearance of urea to be determined.

The children were examined at intervals to assess their growth and development and to determine how long the biochemical disorder persisted. Although some of the children had gone abroad or to distant parts of the country it was possible to pursue these investigations more or less completely in all but one of the 14. This child (Case 14) was admitted to hospital at the age of 4 months with characteristic symptoms, a plasma calcium level of 13·5 mg. per 100 ml., blood urea level of 26 mg. per 100 ml., and no abnormality of the urine. He was treated with a low-calcium milk preparation and the plasma calcium level had returned to normal by the age of 6 months. At 8 months he weighed 16 lb. 5 oz. (7·4 kg.); he was not seen again because his family were nomadic tinkers and could not be traced.

Results

General progress. Three to six years after the onset of idiopathic hypercalcaemia, all 13 children were in good health. They were taking a full mixed diet except for one who was a vegetarian from choice. None was taking cod liver oil or additional vitamin D except that in patent cereal foods. Two of the mothers stated that their children were still slightly constipated, otherwise none of them had any complaints. Some of the children had sat up and walked at the usual times but most had been slightly delayed. Nevertheless, all were sitting up without support by 12 months, and all had taken the first unaided step by 21 months. Intelligence was not formally tested but ordinary clinical observation indicated that all the children except one were well up to average mental development for their ages. The one exception (Case 1) showed slight mental retardation at the age of 5½ years. However, although there had never been radiological abnormalities of her skull, she did have some of the facial characteristics described in the severe type of idiopathic hypercalcaemia (Joseph and Parrott, 1958), namely, a squint, slight epicanthic folds and a prominent upper lip, and thus possibly represented an intermediate form between simple and severe types.

Cardiovascular system. Three children who had had cardiac murmurs during the acute illness had no detectable cardiac abnormality at the most recent examination. Two of the three had originally had T wave abnormalities in the electrocardiogram and these also had disappeared. In none of the 13 children was the blood pressure more than 110/80 mm Hg at review.

Biochemical investigations. All the children had normal levels of plasma calcium at the last recording (range 9·0-11·1 mg. per 100 ml.). Because the level of plasma calcium was determined at irregular intervals in some of the early cases, it was not always possible to be certain exactly when the hypercalcaemia subsided, but the minimum duration was assessed as the time interval between the first diagnosis of hypercalcaemia and the last occasion on which a level of above 12·0 mg. per 100 ml. was recorded; the Table shows the minimum duration of hypercalcaemia in each case. During the original illness, the plasma alkaline phosphatase level was known to be less than 10 King-Armstrong units in seven of the 13 children; all seven had levels above 10 King-Armstrong units at the latest review. Raised plasma cholesterol levels (over 280 mg. per 100 ml.) had been recorded in three of the 13 children but in all three the cholesterol level was less than 230 mg. per 100 ml. at review.

Renal function. In none of the 13 cases did the urine contain protein, sugar or abnormal numbers of cells at the time of review. Tests of renal function were made on the 10 children who had shown evidence of possible renal involvement during the original illness and the results are shown in the Table. In the other three children only concentrating and acidifying abilities were tested. The ages of the children at the time of these tests ranged from 2 years and 5 months to 5 years and 9 months. All the children except one concentrated the urine to a specific gravity of 1·025 or more when fluids were withheld for 12 hours. The one exception (Case 2) concentrated to 1·023; no opportunity arose to repeat the test on this child. All the children were able to acidify the urine to *p*H 5·2 or less, measured with universal indicator and narrow range indicator papers (B.D.H.). In five of the children it was necessary to give ammonium chloride by mouth in a dose of 0·1 g. per kg. of body weight in order to demonstrate this acidifying ability.

The creatinine clearance was more than 75 ml. per min. per 1·73 m.^{2} of surface area in seven of the 10 children tested, while in three it was between 60 and 75. In two of these three (Cases 8 and 12), however, the creatinine determinations were done in a different laboratory, and total Jaffé chromogens

were measured instead of specific endogenous creatinine. The results would thus be expected to be falsely depressed (Roscoe, 1958) and unfortunately the tests could not be repeated in these two children using Hare's method (1950). However, the maximum and standard clearances in Case 12, and the standard urea clearance in Case 8, were all more than 100% of average normal, and it is likely that the true creatinine clearance was considerably higher. One child (Case 4) with a clearance of specific endogenous creatinine of 65·5 ml. per min. per 1·73 m.^{2} was aged 3½ years at the time of the test. There are no satisfactory standards of normal for children of this age, and the clearance value, though low, cannot be regarded as necessarily abnormal, especially as a simultaneous urea clearance test indicated a standard clearance of 117% of average normal.

The standard urea clearance was over 100% of average normal in nine of the 10 children; in three (Cases 2, 11 and 12) the maximum clearance of urea was also determined, each value being above 100% of average normal. The only child with a low standard urea clearance (58% of average normal) was the one suspected of having a form of idiopathic hypercalcaemia intermediate between the simple and severe types, but since the other tests were satisfactory (see Table), this rather low value is of dubious significance.

Growth progress. The heights and weights of the 13 children were measured at intervals throughout the follow-up period, and these, together with measurements made during the illness and any recorded by the mother before admission to hospital, have been plotted on height and weight charts (Figs. 1 and 2). The standards used for these charts are derived from the Oxford Child Health Survey (Acheson, Kemp and Parfit, 1955) and standard deviations (S.D.) from the mean values are shown because only these were published. The −2 and −1 S.D. lines correspond to about the 2·25th and 16th percentiles respectively, and the +1 and +2 S.D. lines to about the 84th and 97·75th percentiles, the error due to the asymmetry of the distribution curve for weight being quite small (Polani, 1959). When weighed, the children were naked or wearing underpants, and height was measured in the standing position (in children over 18 months of age).

Nearly every weight chart shows clearly the deviation of the weight curve during the first two years of life caused by the hypercalcaemic episode and the subsequent return to the original channel. The data on heights are fewer in number and no clear effect on height is demonstrated. In no case is either the height curve or the weight curve still pursuing a course outside the −2 S.D. line. In two cases the height curves are between the −2 and −1 S.D. lines, and in one other case the weight curve is between the −2 and −1 S.D. lines.

Discussion

The tests of renal function did not reveal any significant abnormality in this group of children two to five years after the onset of idiopathic hypercalcaemia. Thus, the ability to concentrate and acidify the urine satisfactorily showed that tubular function was unimpaired. The inulin clearance test, which is generally regarded as a valid measure of glomerular filtration rate, is not easily applicable to young children, and so the clearance of specific endogenous creatinine was used when possible as an indication of glomerular function. This would

TABLE

SUMMARY OF BIOCHEMICAL FINDINGS AND RENAL FUNCTION TESTS IN 14 CASES OF IDIOPATHIC HYPERCALCAEMIA

Case No.	Sex	Maximum Level of Calcium in Plasma (mg./100ml.)	Minimum Duration of Hypercalcaemia (> 12·0 mg./100 ml.)	Maximum Level of Urea in Blood (mg./100ml.)	Minimum Duration of Uraemia (>50 mg./100 ml.)	Tests of Renal Function			
						Time in Years Between Onset and Tests	Creatinine Clearance (ml./min./1·73 m.²)	Minimum *p*H of Urine	Maximum S.G. of Urine
	F	16·8	5 months	135	7 months	5	103·9	<5·0	1·028
	F	14·0	28 months	58	2 weeks	4	115·5	<5·0	1·023
	F	13·9	3 months	76	4 weeks	3½	78·9	<5·0	1·030
	F	13·0	2 weeks	48	nil	3	65·5	5·2	1·028
	F	15·1	1 week	46	nil	2¾	99·9	<5·0	1·030
	F	16·1	4 weeks	60	2 weeks	2½	98·2	5·0	1·026
	F	19·0	2 weeks	63	2 weeks	2½	77·3	<5·0	1·025
	F	16·0	3 weeks	60	1 week	2	64·6	5·0	1·027
	F	13·4	2 weeks	29	nil	3½	—	<5·0	1·029
	F	13·3	1 week	37	nil	3¼	—	5·2	1·025
	M	15·6	3 months	40	nil	5	103·9	<5·0	1·028
	M	13·3	8 months	72	8 months	4¼	62·3	5·0	1·025
	M	14·0	4 weeks	50	nil	5	—	<5·0	1·025
	M	13·5	2 weeks	50	nil	—	—	—	—

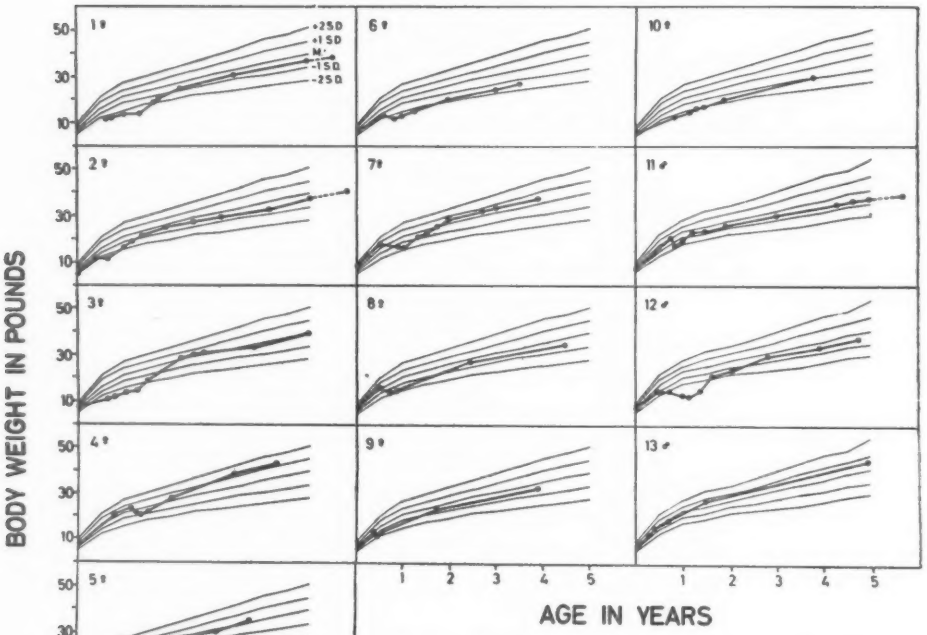

FIG. 1.—Weight charts of 13 children who had idiopathic hypercalcaemia in infancy. Cases 1 to 10 are girls and Cases 11 to 13 are boys. (S.D.=standard deviation: M=mean).

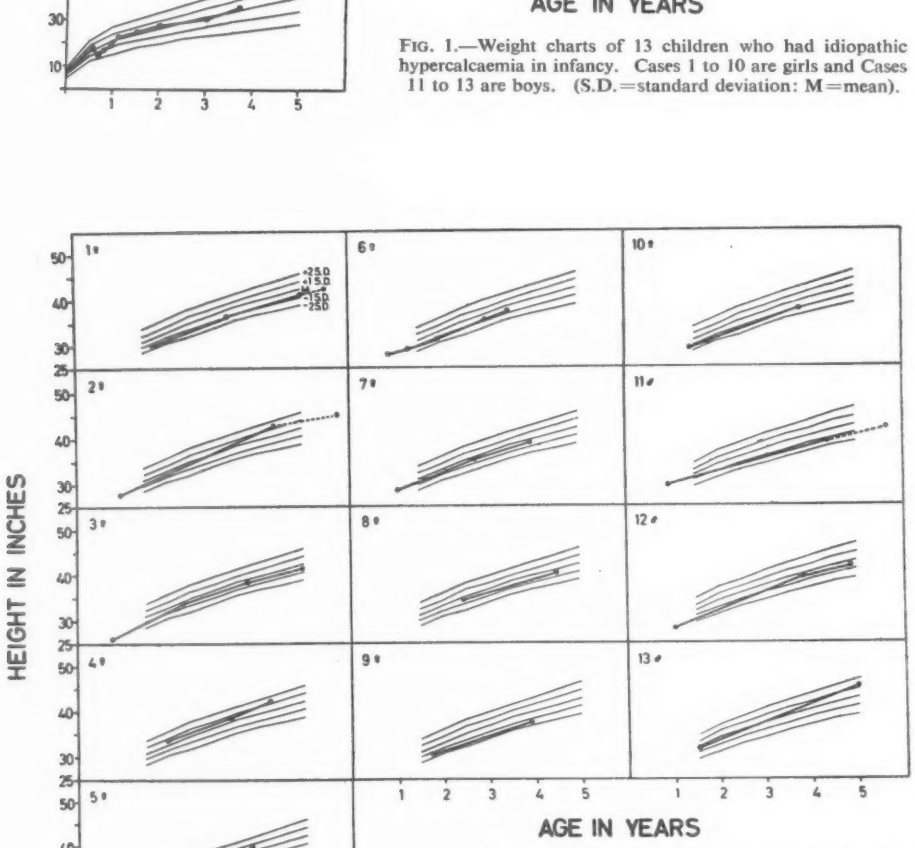

FIG. 2.—Height charts of 13 children who had idiopathic hypercalcaemia in infancy. Cases 1 to 10 are girls and Cases 11 to 13 are boys.

e valid in children with disease affecting the renal ubules (Mattar, Barnett, McNamara and Lauson, 1952), but the evidence indicated that all these children had normal tubular function, and the creatinine clearance was therefore accepted as an approximate measure of glomerular filtration. The values obtained are somewhat lower than those recorded by Ikkos and Ström (1955) for older children, but all fall within a fairly small range and are considered to indicate satisfactory glomerular function.

It is well established that persistent hypercalcaemia can cause renal damage, calculus formation and calcification (Thomas, Connor and Morgan, 1959) and it is therefore remarkable that one child (Case 2), who was known to have had hypercalcaemia for at least 28 months, should have apparently completely normal renal function at the age of 4½ years. In the earliest patients, who were treated by withdrawal of vitamin D alone, the hypercalcaemia was allowed to persist much longer than in the later ones, in whom active measures were taken to reduce the level of plasma calcium. Low calcium diets alone were not always successful in reducing the level promptly but a rapid fall usually followed the administration of cortisone, and this action was sometimes used to maintain the plasma calcium at a lower level until the reduction in calcium intake could become effective.

The way in which cortisone acts is not understood, although its beneficial effect in idiopathic hypercalcaemia of infants may in part be due to reduced absorption of calcium from the intestine (Anderson, Dent, Harper and Philpot, 1954; Morgan *et al.*, 1956). In an attempt to throw further light on the mode of action of cortisone, the level of plasma calcium was measured in four untreated hypercalcaemic infants before, and at short intervals after, a single oral dose of cortisone (Fig. 3). The rate of fall in the plasma calcium level indicates that some mechanism more rapid than the intestinal action must be operating initially. This cannot be a renal tubular effect, since there was no increase in calcium in the urine during these tests. It has been postulated by Cruickshank and Kodicek (1958) that cortisone acts by influencing the metabolism of skeletal tissues and there is indirect evidence that cortisone can inhibit the resorption of bone (Thomas and Morgan, 1958; Morgan, 1959).

The charts for height and weight indicate satisfactory growth progress during the years immediately following clinical recovery from the simple type of idiopathic hypercalcaemia. There is no apparent association between the rate of return to the expected growth channel and the duration or degree of either

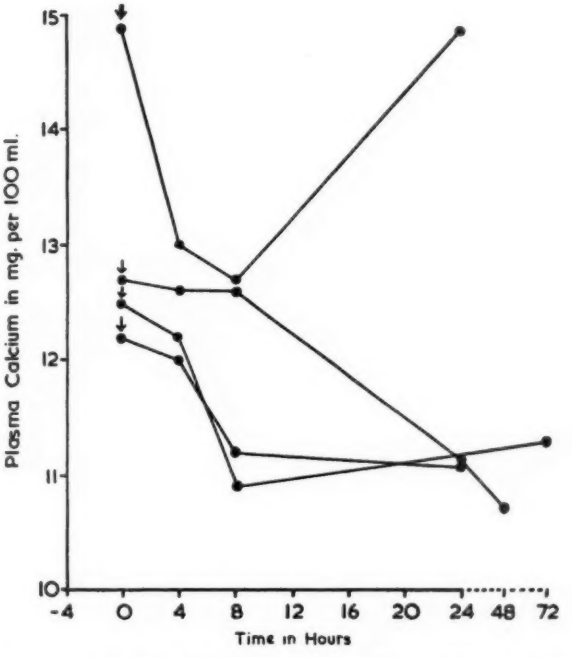

FIG. 3.—The effect of cortisone on the plasma calcium level in four cases of idiopathic hypercalcaemia. (The arrow indicates 25 mg. cortisone acetate given orally.)

the hypercalcaemia or the elevation of blood urea. Thus the child who was known to have had hypercalcaemia for at least 28 months (Case 2) was above average in height. Her weight curve did pursue a course below the mean level, but this was probably not attributable to the prolonged metabolic disturbance, since height as well as weight has usually been affected by persistent elevation of plasma calcium in cases of the severe type of idiopathic hypercalcaemia, as it was also in the patient described by Smith *et al.* (1959), who seems to have had the simple type of idiopathic hypercalcaemia.

This investigation provides evidence in support of the opinions of earlier workers that recovery from the simple type of idiopathic hypercalcaemia is usually complete. Nevertheless, the possibility of unexpected death in the acute stage (Rhaney and Mitchell, 1956), the recognition of cases intermediate between simple and severe forms of idiopathic hypercalcaemia, and the prolonged course occasionally followed by apparently simple cases (Smith *et al.*, 1959), should make one hesitate to give an unreservedly good prognosis for the individual child.

Summary

Thirteen cases of the simple type of idiopathic hypercalcaemia of infants have been followed up

for three to six years after the onset of the illness.

All the children are in good health and all except one are mentally normal, the one exception having certain features suggesting a syndrome intermediate between the simple and severe types.

In all cases the abnormal biochemical findings originally present have disappeared. Simple tests of renal function performed two to five years after the onset did not indicate any residual impairment of renal function.

Although the hypercalcaemic episode caused a marked deviation of the weight curve in nearly every child, the height and weight charts indicate that subsequent progress has been satisfactory.

I wish to thank Professor J. L. Henderson and Dr. James Thomson for permission to include their cases in this study and for their kindly criticism. I am very grateful to Dr. F. L. Mitchell and Dr. H. G. Morgan for the biochemical investigations and for helpful advice. I also thank Miss M. W. Mackenzie for the illustrations.

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PNEUMOMEDIASTINUM AND SUBCUTANEOUS EMPHYSEMA IN STATUS ASTHMATICUS, REQUIRING SURGICAL DECOMPRESSION

BY

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(RECEIVED FOR PUBLICATION NOVEMBER 10, 1959)

Leakage of air into the interstitial tissues of the lungs of sufficient degree to produce pneumomediastinum and subcutaneous emphysema is an uncommon and potentially fatal complication of bronchial asthma in childhood. Another possibly fatal complication of similar causation is tension pneumothorax. It is possible that interstitial emphysema occurs more frequently in severe asthma and allied states than our usual methods of diagnosis allow us to discover, producing additional interference with ventilation by distending and splinting the area of lung involved. This case report and discussion of some relevant literature may serve to illustrate some of these points.

Case Report

A boy, 8 years of age, had had periodic attacks of asthma for four years, some precipitated by hay making and others by dusting of rooms. He had been admitted to this hospital in November, 1956, on the third day of a severe attack in which there was blood staining of the sputum; the attack responded to intravenous aminophylline and oral ephedrine hydrochloride. Skin tests with Bencards reagents showed marked sensitivity to mixed pollens, house dust, horse hair and cat fur. Between January and March, 1957, hyposensitization with a mixed vaccine was attempted, one brief asthmatic attack occurring during the course. A paternal uncle and a grand-uncle were asthmatic.

The present attack had commenced some 20 hours before his admission on April 14, 1957; he had been given approximately 12 subcutaneous injections of adrenalin by his family doctor and a final injection of 0·3 ml. in divided doses by the physician in a district hospital; some ephedrine had been given orally. He had to be brought from an island off the west coast by boat and then 60 miles by road to this hospital. On admission there was marked expiratory and inspiratory dyspnoea, with inspiratory lower costal retraction; the respiratory rate was 55/min., the cardiac rate 160 and the temperature 100° F. There appeared to be acute-on-chronic pulmonary emphysema and the cardiac dullness was obliterated. The blood pressure was 140/90 mm. Hg, the weight 49 lb. Small amounts of blood-stained sputum were expectorated with difficulty and cough was forcible and distressing. Aminophylline 0·125 g. was given intravenously on two occasions with temporary relief; 500,000 units of intramuscular penicillin and ½ gr. of phenobarbitone were given, and repeated at 12 hour and six hour intervals respectively.

Four hours after admission subcutaneous emphysema was observed above the clavicles, quickly spreading to the neck, cheeks and axillae; the blood pressure was then 150/90 mm. Hg. Three hours later the respiratory distress became more marked and was accompanied by cyanosis despite an efficient oxygen tent. The chest was almost fixed in the maximal inspiratory position, the neck and upper thoracic veins were engorged, the pulse volume was diminished and showed paradoxical respiratory variation.

Cortisone acetate 100 mg. was given intramuscularly. Pneumomediastinum was suspected and confirmed by portable radiographs (Figs. 1 and 2). As the boy's condition was critical, horizontal incisions of about 1½ in. were made under local anaesthesia above each clavicle, about eight and a half hours after admission. Exploration with sinus forceps through the incisions allowed release of air under pressure with marked relief of the distress and of the venous distension. The pulse volume improved and the boy rested comfortably. Gradual resolution of the asthmatic attack followed, the subcutaneous emphysema taking some days to disappear; several exacerbations of the asthma occurred before his discharge nine weeks later. The boy has since been admitted with two severe attacks without recurrence of any observable pulmonary air leak.

Discussion

Peterson (1947) states that mediastinal emphysema was first described by Müller in 1888, while Matts (1957) states that Laennec (1827) described it under the name of 'interlobular emphysema'.

Macklin and Macklin (1944) discuss the subject of non-surgical interstitial emphysema of the lungs and mediastinum exhaustively, and they maintain

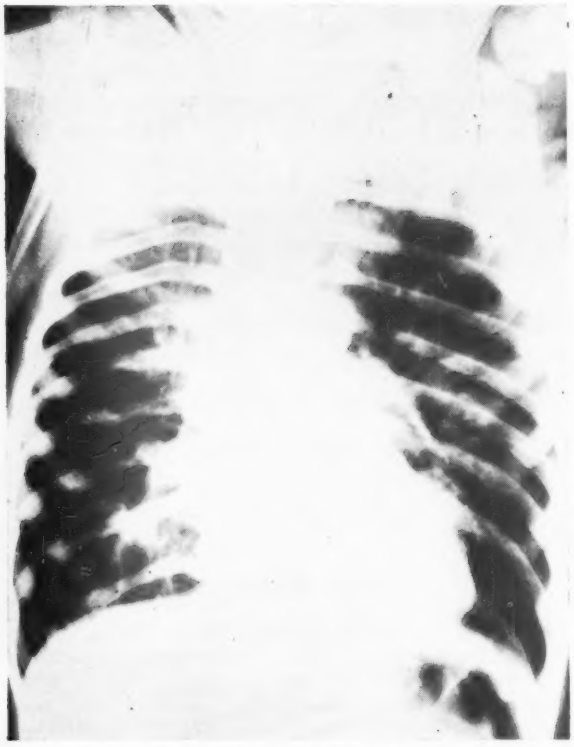

FIG. 1.—Portable antero-posterior film of chest showing distension of lungs, some infiltration of both upper lobes, mainly right, a translucent ring of air surrounding the aortic knuckle and air bubbles in left axilla.

FIG. 2.—Portable lateral film of chest showing large volume of air trapped between heart and sternum, outlining what is probably the thymus. The contrast between the small (presumably compressed) heart and the distended thorax is striking.

that the basic requirement for alveolar rupture and leakage of air into the interstitial tissues of the lung is a pressure gradient from the alveoli to the perivascular sheaths. The pressure gradient may arise from over-inflation of the lung or lowering of vascular pressure; an example of the former, would be compensatory over-inflation of the lung surrounding an area of atelectasis, and of the latter, would be pulmonary embolism. In the majority of instances of interstitial emphysema there is also an increase in the alveolar pressure. Over-inflation of lung may be localized, as in the lung adjoining an atelectatic area or in lung distal to a ball valve bronchial obstruction. Generalized over-inflation appears to cause most cases of air leak, the most common examples being severe expiratory dyspnoea as in bronchial asthma, forceful coughing, severe straining as in lifting of heavy weights or during labour, other examples being forceful resuscitation of the newborn infant or anaesthetized patient. Other examples of interstitial emphysema in which various factors operate and may combine are neonatal atelectasis, obstructive laryngitis, tracheotomy, pertussis, bronchial foreign bodies, severe exercise, lung blast and caisson disease. Pulmonary infection appears to be a factor in many cases, presumably by weakening the alveolar wall, and combined with forceful cough is probably the cause of interstitial emphysema in influenza and measles.

Once air has leaked from the alveolus, if the pressure gradient is maintained, as by persistent dyspnoea and/or coughing, the air usually tracks centrally along the vascular sheaths to the lung root and mediastinum, as Macklin and Macklin (1944) have shown both by experiment and in autopsy material; it may also track peripherally to the subpleural space. The interstitial emphysema may both distend the lung, reducing its mobility and thus interfering with ventilation, and interfere with the pulmonary circulation by compressing blood vessels. When air reaches the mediastinum in large quantities, and does not readily find egress, a tension pneumomediastinum is produced, which impedes venous filling of the heart and thus further restricts the pulmonary, as well as the systemic, circulation; marked venous distension of the neck, head and trunk will occur. Electrocardiographic changes

have been reported (Master, Kalter and Dack, 1941). To these effects will, in many cases, be added interference with ventilation by local or generalized alveolar emphysema and later by pulmonary infection.

From the mediastinum air may escape into one or both pleural cavities, into the tissues of the neck and thence to the head and trunk, or into the retroperitoneal space from which it may rupture into the peritoneum; escape of air by one or other of these routes usually acts as a safety valve, preventing cardiac tamponade, although the other hazard of tension pneumothorax may be produced. Macklin and Macklin (1944) believe that varying degrees of interstitial emphysema may frequently occur in such conditions as severe asthma and may play a significant part in the dyspnoea; although agreeing with other authors that such leakage of air is usually benign, due either to its limited extent or to the operation of the 'safety valve', they emphasize its potentially fatal nature.

Norman (1957) in describing a boy of 21 months who had a pneumothorax and subcutaneous emphysema complicating bronchial asthma on two occasions, found 30 published cases of subcutaneous emphysema in asthma. Two were fatal, and in two others incision of the skin in the neck to allow escape of air was necessary. Macklin and Macklin (1944) cite reports of other fatal cases of asthma where death was attributable to pneumomediastinum, pneumothorax, or both, in the absence of subcutaneous emphysema.

Recognition and Management. Macklin and Macklin (1944) maintain that the presence of subcutaneous emphysema in the neck presupposes a pneumomediastinum, which should also be suspected in severe asthma without subcutaneous emphysema if there is marked venous distension of the neck, head and upper thorax, or other evidence of cardiac tamponade such as paradoxical pulse with falling blood pressure. In patients old enough to complain, there may be substernal pain of anginal nature, abdominal pain, or a feeling of fullness in the upper chest and neck. Obliteration of cardiac dullness, bulging and tympany of the upper sternum are signs of pneumomediastinum but will be more commonly due to acute generalized pulmonary alveolar emphysema. Systolic crunching or crackling sounds, best heard with the patient in the left lateral position (Hamman, 1937) are said to be diagnostic of air in the mediastinum. Lateral radiograph of the chest is the most valuable procedure, the presence of air between the cardiac and sternal shadows being diagnostic; air may also be seen surrounding the heart in postero-anterior views. Increasing cyanosis and signs of reduced cardiac output, with weakening peripheral circulation will call for urgent decompression of the trapped air in the mediastinum. If air is confined to the mediastinum, needling and under water drainage are indicated. When subcutaneous emphysema is present, incision of the skin in the suprasternal notch is usually adequate, exploration with sinus forceps or gloved finger being continued until sufficient air has been released. Schrire and Schrire (1952) described a 6 in. horizontal incision in the suprasternal notch, vertical incision of the platysma, elevation of the thyroid and insertion of a finger down either side of the trachea to facilitate escape of air, but this procedure should hardly be necessary in most cases. Bilateral incisions, as in the present case, would not seem to be necessary. Following decompression, the wound should be left open and covered with loose gauze, broad spectrum antibiotic cover being provided.

Summary

Pneumomediastinum and subcutaneous emphysema complicating severe asthma in an 8-year-old boy are described; release of air by means of incisions of the skin in the neck was necessary due to signs of cardiac tamponade.

Some of the relevant literature is reviewed, including an acceptable theory of production of emphysema of interstitial pulmonary tissues, mediastinum and subcutis.

Recognition and management of pneumomediastinum are briefly discussed.

I wish to thank Mr. D. Kneafsey for reading and criticizing this paper and for his help with later interpretation of the radiographs; also Dr. John Horan for his case notes and help with management of the patient.

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Addendum

A 4-year-old girl was admitted in March, 1960, in the third day of an attack of bronchopneumonia, with subcutaneous emphysema in the neck of six hours' duration. Within a few hours the emphysema had spread to the cheeks, left temple and left lower eyelid, both axillae, and had formed a tense V-shaped swelling over the upper chest with its apex at the sternal angle. There was a forceful dry cough with some expiratory difficulty, wheezing and grunting, suggesting predominant involvement of the bronchioles. Pneumomediastinum was shown by many crunching and bubbling sounds with respiration over the whole sternal area and by very well marked praecordial systolic 'crunching' sounds; the pneumomediastinum was confirmed by radiography. The child was not very distressed at any stage and there was no overfilling of neck veins, but there was thought to be some diminution of pulse volume during inspiration. An interesting finding was regular lowering of the amplitude of the ventricular complexes in the E.C.G. during inspiration, this being most marked in leads V_1 and V_4R, without any other abnormal finding. The cardiac rate averaged 150 per minute for the first few hours, and no fall in blood pressure occurred. It is presumed that the E.C.G. findings were due to compression of heart or great vessels, as they had become less marked some days later, and had gone two weeks later.

It was not necessary to decompress the emphysema and this had almost completely disappeared five days later. The respiratory infection responded satisfactorily, intramuscular penicillin being given for eight days. Radiographs showed some pulmonary distension and slight infiltration consistent with a diffuse bronchopneumonia, in addition to air bubbles in soft tissue and mediastinum.

A further interesting feature in connexion with this case is that her brother was admitted to the Fever Department of this hospital in November, 1954, when aged 5 years (under the care of Dr. B. J. O'Driscoll) with subcutaneous and mediastinal emphysema complicating measles bronchopneumonia, the condition subsiding uneventfully with penicillin treatment. The occurrence in siblings of pulmonary air leakage complicating respiratory infections might be due to a common developmental anomaly of the lungs predisposing towards air leakage with certain types of respiratory involvement. It might equally well be coincidental.

CREATINURIA IN MÖBIUS' SYNDROME

BY

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(RECEIVED FOR PUBLICATION OCTOBER 19, 1959)

Since the first description by Harlan (1881) of a patient with bilateral congenital facial palsy and external rectus palsy, several excellent reviews of the Möbius' syndrome have been published, in which various theories regarding the aetiology of the condition have been discussed.

Möbius (1892) believed that the mixture of cranial nerve lesions was due to a toxic or degenerative process. Heubner (1900) described the pathological findings in one case, in which the ganglion cells were absent from the motor nuclei of certain cranial nerves, with poor development of the formatio reticularis, olives and pyramidal tracts. Rainy and Fowler (1903) considered the primary pathology to be in the muscles, with secondary degenerative changes in the nuclei.

The bizarre combinations of cranial nerve lesions, and the associated somatic anomalies have intrigued later writers. Henderson (1939) reviewed the condition, describing the typical findings. Paralysis may be complete or incomplete, unilateral or bilateral and most commonly involves the muscles of the face especially in the upper half. External rectus palsy is common, while the muscles supplied by the third, fifth and twelfth cranial nerves are occasionally affected. Club foot occurs in one third of the cases, and defect of the pectoralis major muscle with mammary hypoplasia is a common associated anomaly. Poor general muscle development may also occur. Deformities of one hand or arm and of the ears and nose, absence of the lacrymal caruncles and glands, micrognathos, a high arched palate, vasomotor disturbances and mental defect have all been recorded. This writer discussed the analogy of the Bonnevie-Ullrich syndrome as one mechanism to account for the widespread somatic defects, but could not associate this with agenesis of cranial nuclei. Evans (1955) pointed out that all the major defects are of structures which are differentiated at the end of the second month of intra-uterine life, and considered that the primary pathology was probably in muscle. Sprofkin and Hillman (1956) discussed the similarity to Werdnig Hoffman and Oppenheimer's disease.

Two cases of Möbius' syndrome are presented in this paper. Biochemical investigations were carried out to see if any light could be thrown on the aetiology of the condition.

Case Reports

Case 1. R.W., a boy, was born at home to a healthy multigravida. The labour was normal and at term (he weighed 6 lb.), but as he failed to breathe normally he was transferred to the Sorrento Premature Baby Unit for resuscitation.

On admission he had infrequent gasping respirations, a poor colour, poor muscle tone and excessive pharyngeal mucus. An intracranial birth injury seemed the most likely diagnosis; his appearance was odd even at this stage with marked scaphocephaly, micrognathos, low set ears, an absent left nipple and bilateral talipes equinovarus. His expressionless face was thought to be part of the generalized hypotonia.

The baby survived, unexpectedly, and sub-dural taps and a lumbar puncture did not support the original diagnosis. He could not suck and feeding remained a formidable task throughout his life. It gradually became obvious that he had bilateral facial palsy, bilateral external rectus palsy and probably weakness of some of the external ocular muscles supplied by the third cranial nerve. The intrinsic ocular muscles and the superior oblique muscles were unaffected. The masseters, the pterygoid muscles and the palatal muscles were all weak and later developed contractures. His general muscle development was poor, and he developed a marked thoracic kyphoscoliosis. The left pectoralis major was absent. There were marked epicanthic folds and he did not secrete tears. There was a complete absence of facial expression and a severe dysarthria, so that a gurgle of laughter was indistinguishable from a cry of rage, apart from his change of colour. He did not learn to sit or stand or to speak, but this seemed to be due to muscle weakness rather than to mental defect.

He made slow progress until the age of 18 months (see Fig.), but the contracture of the masseters increased the feeding difficulties and led to frequent aspiration pneumonia. He died at the age of 22 months from a respiratory infection.

FIG.—R.W., Case 1, aged 18 months.

The serum electrolytes, calcium and phosphorus, urea and proteins were normal on several occasions. The urinary amino acid chromatogram was normal. Radiographs of the skeleton showed no defect apart from mandibular hypoplasia.

At the age of 1 year the urinary creatine was 59 mg./100 ml. (approximately 34 mg./kg./day), and the urinary creatinine 38 mg./100 ml. (approximately 22 mg./kg./day), creatine : creatinine ratio, 1·55.

A post mortem examination showed death to be due to acute bronchitis. There was generalized hypoplasia of the muscles. There was no macroscopic abnormality of the central nervous system, and preliminary examination of celloidin blocks of various areas of brain, stained by the Nissl method, showed no anatomical abnormality.

This child had a paternal uncle who died at the age of 2 years and apparently 'he looked just like R.W.'.

Case 2. S.M., a boy, was born at St. Helier Hospital to a healthy multigravida at full term and weighed 7½ lb. There was hydramnios, but the delivery was straightforward. The baby was limp and respirations were not established until 25 minutes after birth. An intracranial birth injury was suspected and he was nursed in oxygen for the first 12 days of life. He developed sclerema neonatorum. He required tube feeding for the first six weeks of life, but then sucked well and has been breast fed since.

The lack of facial expression and generalized hypotonia, noticed at birth, persisted and, when at the age of 4 months he developed a left talipes equino-varus, the diagnosis of Möbius' syndrome seemed established. There is now bilateral facial paralysis with some sparing of the orbicularis oris. The cry is strangely monotonous but the remaining muscles supplied by the cranial nerves do not appear to be affected. The muscles of the neck, trunk and legs are poorly developed, but his arm movements are normal for his present age of 6 months. He has a high arched palate, slight micrognathos and low set ears. The equinus deformity has been kept under control with Denis Browne splints, but the forefoot varus persists and as the tendons on the anterior aspect of the left ankle cannot be felt, the tibialis anterior muscle is probably absent.

Full biochemical investigations have not been undertaken. At 5 months of age the urinary creatine was 9·1 mg./kg./day and the creatinine 6·2 mg./kg./day, creatine : creatinine ratio, 1·48.

Discussion

Creatinine is normally produced in the body from creatine by enzymic action during muscular activity. This mechanism is more efficient in adult men than in women and children, in whom a degree of creatinuria is normal. However, the excretion of creatine should not exceed 30-40% that of creatinine. In normal infants the excretion of creatine is 0-7 mg./kg./day, and of creatinine is 11-14 mg./kg./day (Nitowsky, Gordon and Tyson Tildon, 1956). Creatinuria is found in myasthenia gravis, and in the muscular dystrophies in which levels of 8-11 mg./kg./day have been recorded (Wilkins, 1957).

The high levels of creatinuria found in the two infants recorded, seem to indicate some abnormality of muscle metabolism. The very high level in Case 1 may demonstrate the severity of the affection.

The clinical similarity of the Möbius' syndrome to amyotonia congenita has been noted, and this biochemical abnormality lends support to the opinion that the syndrome is a myopathy rather than a neurological defect. The absence of the pectoralis major and the nipple on one side and the micrognathos in Case 1, the high arched palate in Case 2, and the many associated somatic defects described in the syndrome show that this is not solely an enzyme abnormality.

Although all the structures affected in this

syndrome are differentiated at the end of the second month of intra-uterine life, it is unlikely that a permanant biochemical defect could be produced by an environmental 'insult' to the foetus at this stage of development. Thus it seems unlikely that the syndrome could follow damage by migrating myelencephalic blebs as in the Bonnevie-Ullrich syndrome. Possibly an abnormality of second month 'organizers' and an enzyme defect could be produced by a single genetic mutation. The occasional finding of a familial incidence would seem to support this view of the aetiology of the syndrome.

Summary

Two cases of Möbius' syndrome are described. The finding of marked creatinuria in both infants suggests that the muscle weakness is due to a myopathy rather than to nuclear agenesis. A single genetic mutation might produce an enzyme defect and abnormal second month 'organizers'.

I wish to thank Dr. V. Mary Crosse and Dr. J. N. O'Reilly for permission to publish their cases, Dr. A. H. Henley and the staffs of the biochemical laboratories of the Little Bromwich General Hospital and St. Helier Hospital for their help with the biochemical investigations, and Dr. J. Hoult of Dudley Road Hospital, who performed the post mortem examination in Case 1.

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PROSTATIC ABSCESS IN THE NEWBORN

BY

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(RECEIVED FOR PUBLICATION OCTOBER 26, 1959)

During the past 14 months we have been able to confirm the occurrence of pyogenic infection of the prostate gland in three neonates admitted to one surgical unit of this hospital. As one case terminated fatally before we had appreciated the existence of such a clinical entity, it is desirable that it should be brought to the notice of others who may be confronted with a similar problem.

There is a current belief that the prostate has little clinical importance during infancy, and references are few. Bodian (1957) described two fatal cases of urinary retention due to fibroelastosis. Prostatic infection in older children has been reviewed extensively by Campbell (1937), and Winsbury-White (1949) showed such a possibility in a 9-year-old boy in whom the passage of a urethral catheter produced a purulent urethral discharge, but the diagnosis was not supported by any other confirmatory findings and there was no evidence of the periprostatic haematoma formation recently reported by Williams and Martins (1960). The following instances were in newborn babies.

Case Histories

Case 1. A male child delivered at full term, weighing 6½ lb., was admitted with retention and dribbling incontinence. Catheterization was followed by an issue of almost pure pus under pressure, and, from this, penicillin insensitive *Staph. aureus* was subsequently isolated.

Pyuria persisted for a few days but micturition soon assumed the characteristic infant pattern, the napkins being wet intermittently, and not continuously as before. Radiographic investigation after an interval revealed no evidence of obstructive uropathy.

Case 2. A male child weighing 9 lb. 11 oz. was discharged from a maternity hospital following a caesarian birth, but subsequently re-admitted as the mother had noticed increasing dysuria, continuously damp napkins, and dribbling incontinence. He was 14 days old when he was admitted to this hospital with diarrhoea, bladder distension, and complete retention of urine. There was some thick pus in the urethra, and as no urine could be withdrawn by catheter, the bladder was drained by inserting a wide bore needle supra-pubically. Very gross pyuria was noted, and penicillin resistant *Staph. aureus* was subsequently grown from the specimen. This procedure gave considerable relief, and it seemed probable that the abscess had undergone spontaneous rupture into the bladder, but micturition did not improve, and lacked the characteristic decisiveness of infancy. Attempts to catheterize were unsuccessful as the instrument was held up in the posterior urethra, and urethrography showed a constant reduction in calibre in this area, which the radiologist reported as consistent with congenital stricture (see Figs. 1 and 2.)

This was divided by open operation, and for the past year the infant has remained well with unimpaired micturition. Pyelograms show the upper renal tracts to be within normal limits.

Case 3. A male infant, aged 3 weeks, who had been fretful from birth, was admitted to Dr. Hutchison's wards, and later transferred to the surgical side on account of increasing abdominal distension.

There was slight oedema of the lower abdominal wall, and a rather diffuse mass was palpated anteriorly on rectal examination, but the nature of this was not appreciated and a provisional diagnosis of neonatal Hirschsprung's disease was made. A distended bladder was emptied by catheter on the operating table, but unfortunately no significance was attached to this, as it is a fairly common preoperative requirement. Laparotomy revealed distension of large bowel and terminal ileum and transverse colostomy was performed. On the following day the infant died of septicaemia and an extract of the post mortem findings is as follows:

'The lower half of the small intestine and the whole of the large intestine show marked gaseous distension.

'The lungs show patchy areas of consolidation and haemorrhage.

'Both kidney pelves are moderately congested, but are not dilated, and the ureters are normal in appearance. The bladder is markedly distended. There is obvious congestion of the serosa and on opening the bladder very purulent looking urine is seen to fill the cavity. Similar purulent urine can be expressed from the urethra on compressing the bladder. At the base of the bladder a large abscess cavity measuring approximately 3 cm. by 6 cm. surrounds the urethra and spreads upwards behind the bladder and between it and the rectum (Fig. 3). The abscess appears to have arisen in the prostate.

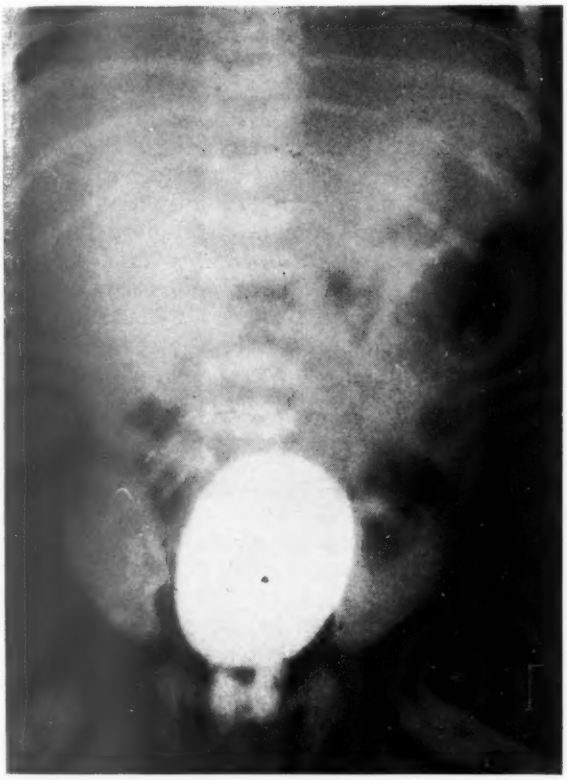

FIG. 1.

FIG. 2.

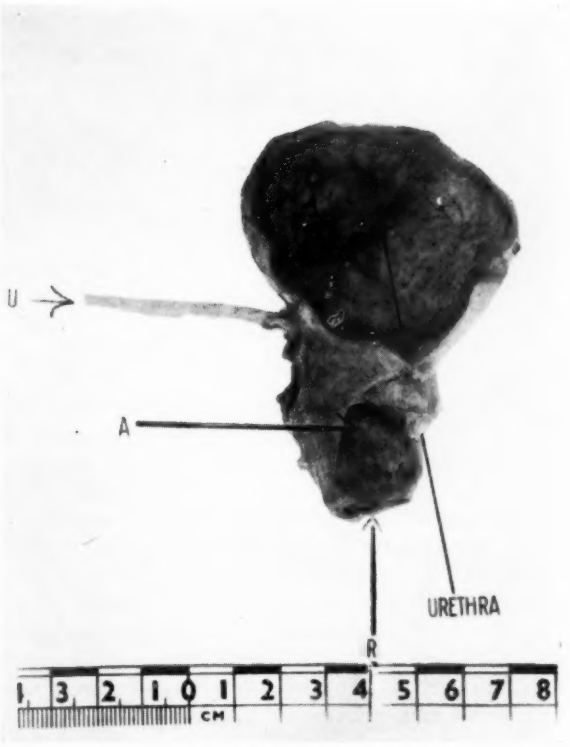

FIG. 3.

FIG. 1.—Case 2, urethrogram of prostatic abscess.
FIG. 2.—Case 2, urethrogram of residual prostatic abscess.
FIG. 3.—Case 3, abscess cavity (A) between urethra and rectum (R).
FIG. 4.—Urethrogram of child's prostate to show distension by back pressure from obstruction in distal urethra.

FIG. 4.

'In the colon, ganglion cells are present in normal numbers.'

HISTOLOGY. 'The abscess is chronic in type and beyond the pyogenic membrane there is a narrow rim of prostatic tissue, with pus cells in some of the adjacent glands. There is some diffuse infiltration of the bladder wall with inflammatory cells. The kidneys show early pyelonephritis.'

BACTERIOLOGY. A swab from the prostatic abscess and a piece of lung grew penicillin resistant *Staph. aureus* and lactose fermenting coliforms in each instance, the former being sensitive to chloromycetin and furadantin and resistant to achromycin.

Discussion

Three factors may be considered to have some bearing on the development of acute neonatal prostatitis. Firstly there is the infection, to which all the newborn are at risk. It is stated by White and Dennison (1958) that in neonatal osteitis the staphylococcus has been found resistant to penicillin in over 80% of cases admitted to the Royal Hospital for Sick Children, Glasgow, and Dennison (1959) has observed the incidence of penicillin resistance to be highest in hospital-born babies. The three cases described here were all born in maternity units and penicillin resistant staphylococcus was responsible in each.

The remaining factors may be considered to play a role in determining the location of the abscess. At birth there is the squamous metaplasia of the epithelium of the utricle, prostatic urethra and prostatic glands which undergoes regression during the first week of life (Smith, 1945). The third factor, that of obstruction to the urinary outflow, was well shown in Case 2. Potter (1952) has emphasized that congenital malformation with stasis predisposes to acute infection of the urinary system, and the effect of blockage distal to the prostate is demonstrated in the accompanying photograph (Fig. 4) where we have been able to show a dilated but otherwise normal infant prostate resulting from back pressure.

Diagnosis. There should be little difficulty in diagnosis once the condition becomes established as a clinical entity. After catheterization of a distended bladder in any male infant, one should not omit rectal examination. A cystic swelling may be felt below and in continuity with the bladder. Where rupture of the abscess occurs spontaneously, or after the use of a catheter, nothing further may be required, but urethrography should be performed, and this will show the residual abscess and indicate the site of stricture, if present. Pyogenic infection of the infant prostate may not be the rarity the literature would suggest, for spontaneous rupture into the bladder, followed by temporary pyuria, and in many cases by complete remission, is a possibility that could be overlooked. Peri-urethral abscess, secondary to infection of urethral glands has been observed in infants by White (1959) and may have originated in this manner.

Treatment. This is essentially surgical. The perineal approach to the tough distended capsule of the prostate requires special experience of paediatric urology and drainage of the infected bladder by perineal urethrostomy may be advisable, and should be continued, where necessary, until co-existing urethral stricture has been dealt with.

Summary

Three cases of acute staphylococcal prostatitis causing urinary obstruction in neonates are described. Clinical, radiograph and post mortem findings are described.

Possible causative factors are discussed and treatment indicated.

My thanks are due to Mr. Wallace Dennison who has helped me, throughout, with all cases, to Dr. Philip Rawson for radiographs and to Dr. Alistair M. MacDonald for photographs and post mortem report.

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ILIAC VEIN OBSTRUCTION DUE TO A RETROPERITONEAL ABSCESS

BY

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(RECEIVED FOR PUBLICATION OCTOBER 20, 1959)

The occurrence of iliac vein obstruction due to a retroperitoneal abscess in infants is a rare phenomenon. This presentation of a case may be of value in the diagnosis of other cases.

Case Report

L.M., a newborn white female infant, was admitted on February 8, 1959, to Cleveland Metropolitan General Hospital as a premature home delivery. Her birth weight was 1,840 g. (4 lb.), and expected date of delivery was March 18, 1959. The mother did not have antenatal care. On the second day in hospital the baby was noted to be jaundiced. The mother's blood was group A Rh positive and the baby was group O Rh positive. On the fourth day in hospital the maximum bilirubin level was 19 mg.%. The baby did not feed well. There was no evidence of septicaemia as indicated by a negative urinalysis and normal spinal fluid. On the tenth day a femoral venipuncture was done for blood cultures and serum chemistries. The side from which the blood was drawn was not recorded. The blood cultures were negative and all the serum chemistry was within the normal range.

At the age of 25 days, swelling of the right thigh and foot was noted. The leg was oedematous and showed some discolouration. Some areas over the thigh were fluctuant but no localizing abscess was present. Inguinal nodes were not palpable. The measurements above the knees were: right 14 cm., left 12 cm. The W.B.C. was 26,850/c.mm. (neutrophils 70%). An infection was suspected. Radiograph of the hips revealed no evidence of osteomyelitis of the hip or any intra-articular fluid. The fluctuant area was aspirated but no free fluid was obtained. Material from the needle was cultured and blood cultures were also drawn. The blood cultures were negative but the aspirate grew haemolytic *Staphylococcus aureus* coagulase positive; resistant to penicillin; sensitive to erythromycin, streptomycin, kanamycin, furadantin, neomycin, chloramphenicol. Nose culture grew *Staphylococcus albus*. Chloramphenicol treatment was started.

On the 26th day in hospital circumferences of the thighs were: right 14·5 cm.; left 12 cm.; W.B.C. 18,500 c.mm. (neutrophils 54%). The right leg seemed to become more oedematous and on the 30th day measured 15 cm.; left 12 cm.; W.B.C. 25,500 c.mm. (neutrophils 83%). The diagnosis of thrombophlebitis was entertained at this point. The infant was continued on chloramphenicol and clinically there was no change in the condition of the leg. She held the right leg abducted and externally rotated and resented having the leg moved. No abdominal masses were palpable. Rectal examination was normal. A low grade fever with temperatures of 37° C. to 38° C. now appeared.

On the 32nd day an intravenous pyelogram was done, but no pathological process was noticed. A cystogram on the 33rd day showed no evidence of displacement or filling defect of the bladder. Phlebograms were not done. A mass was now palpable in the right lower quadrant deep in the pelvis extending to Poupart's ligament. Rectal examination revealed a bogginess in the area of the right iliopsoas muscle. The diagnosis of retroperitoneal abscess with iliac vein obstruction which had been previously entertained was now confirmed.

On the 34th day a retroperitoneal dissection was done with counterincision of the right thigh and 20 ml. of greenish yellow pus was removed. Gram stain revealed gram positive cocci and culture grew haemolytic *Staphylococcus aureus* coagulase positive; resistant to penicillin, streptomycin, erythromycin, chloramphenicol; sensitive to neomycin, kanamycin, furadantin. Pus was obtained in the operative field by pressure on the thigh and a guide introduced behind the psoas fascia anteriorly extended to the upper and medial aspect of the right thigh. 60 ml. of blood was given to the infant. On the second postoperative day measurements of the thighs were: right 12·75 cm., left 11 cm.

The chloramphenicol was discontinued on the 46th day. The infant now weighed 2,660 g. (5 lb. 14 oz.). She was discharged at the age of 2 months, completely well and when seen at the out-patient clinic two weeks later the leg was normal in size compared to the left and the wound had healed. At the age of 6 months the leg and hip were normal. Radiograph of the hip showed no dislocation or destruction of the head of the femur.

Discussion

The diagnosis of iliac vein obstruction due to a retroperitoneal abscess should be considered when an infant presents with an oedematous leg and dis-

tended veins. In 1957 Grunwaldt and Tomsovic reported two cases in male infants secondary to circumcision, and since then no further reports have appeared in the literature. In the differential diagnosis, thrombophlebitis, hip disease or, if it follows a femoral vein puncture, an infected haematoma must also be considered. The diagnosis of a retroperitoneal abscess can be made by the palpation of a mass in the lower abdomen and on rectal examination. Special investigations such as intravenous pyelography, cystograms and phlebograms may be confirmatory.

Once the diagnosis has been made surgical drainage is the only method of treatment. The aetiological organism can then be determined and appropriate antibiotic therapy instituted. It was distressing to note that the organisms isolated from this case were *Staphylococcus aureus* coagulase positive, and that they were resistant to erythromycin and chloramphenicol, the drugs most frequently used for staphylococcal infections.

The pathogenesis of this infection presents many problems for consideration. In this report we must consider the site of femoral vein puncture as the route of introduction of the infection.

Grunwaldt and Tomsovic (1957) report two cases of iliac vein obstruction in male infants both aged 3 weeks. They conclude that the primary site of infection was the circumcision site. Inguinal nodes were palpable in their cases. This suggests that the retroperitoneal infection in those cases was possibly related to skin infection, most likely the penis.

Gross (1953) reports that in some cases of iliac adenitis the portal of entry of the infection may be found on the leg or around the arms, but the initial lesion is often healed by the time the patient presents with abdominal complaints or limp. In most cases the infection skips the femoral and inguinal glands and lodges solely in the iliac group. The age range of the 20 cases reported varies from 1 to 11 years. Sex incidence is not discussed.

Reference is made in the literature to obstructive anomalies of the iliac veins with growth shortening of the ipsilateral leg (Peck, 1957). The obstruction can be either an acquired or developmental disease represented by adhesions in the retroaortic portion of the vein, or pathology due to congenital valves or septa.

Ross (1954) mentions a case of osteomyelitis of the hip with complete destruction of the head and neck of femur following a femoral venipuncture in a premature infant, but concludes that the infection of the hip resulted from a haematogenous spread from a distant focus rather than from a venipuncture in the region of the hip.

Howard (1957) reports five cases of sepsis in normal and premature infants with localization in the hip joint, but does not relate this to femoral venipuncture. He concludes that in one case the probable portal of entry of the infection was from an injection of vitamin K. Three of his five cases had received vitamin K and other subcutaneous injections.

Neuhof and Arnheim (1944) quote two cases of infected haematomas as a source of infection with formation of iliac retroperitoneal abscess.

Bosch, Kengeter and Beling (1950) discuss femoral venipuncture in 100 adult patients. They list the possible complications, namely, injury to femoral vein, penetration of a viscus in the presence of unrecognized femoral hernia, haematoma, abscess or cellulitis, penetration of psoas abscess, local ecchymosis, thrombophlebitis, phlebothrombosis or arteriovenous fistula.

Sieber and Ferguson (1959) review some of the surgical and orthopaedic aspects of infections in newly-born and young infants. From 1940 to 1957 31 cases, who had had bacterial infections of bones and joints, were found. Nine of these 31 infants had septic hips. They mention femoral vein puncture as an aetiological factor in the localization of infection in the hip joint of four infants.

This report differs from any of the previous cases described in that this occurred in a female infant, no intramuscular or subcutaneous injections were given, and the only probable portal of entry of the infection was the femoral venipuncture.

The jaundice was considered as physiological in a premature infant. In this case there was no evidence of any septicaemia as indicated by the negative blood cultures on the 10th and 25th hospital days. A haematoma at the site of venipuncture or a thrombophlebitis may possibly have been a predisposing factor in the development of this infection. It is virtually impossible to prove that the femoral venipuncture resulted in this retroperitoneal abscess, but it would seem that this is the most likely portal of entry of the infection.

When one asks other paediatricians if they have ever encountered any complication of femoral venipuncture, they may recall some cases of hip infection or osteomyelitis of the femur, but they cannot prove that this was a complication of femoral venipuncture.

In this hospital femoral vein punctures are regarded as hazardous procedures. In the first few days of life the umbilical vein can easily be entered and many paediatricians feel that adequate blood samples can be obtained by this route. It has been disturbing to note the number of positive blood

cultures obtained before starting exchange transfusions, and an investigation was conducted to determine the feasibility of using this procedure for routine blood cultures in newborns. In a report (Lipsitz and Cornet, unpublished) it will be shown how 15 out of 33 blood cultures obtained from healthy newborns were contaminated with the same organisms as cultured from the umbilical stump. It is strongly recommended that this procedure should not be used.

Summary

This report is of a case of retroperitoneal abscess with iliac vein obstruction in a premature white female infant aged 25 days. The diagnosis was made on palpation of a mass in the right lower quadrant and rectal examination revealing some bogginess on the right side. It is most likely that the portal of entry was from the site of a femoral vein puncture.

The possible hazards of femoral venipuncture are discussed. Reference is also made to the validity of blood cultures obtained via the umbilical vein.

A review of some of the cases of hip joint pathology in premature infants does not relate the infection to venipuncture, but more likely to subcutaneous and intramuscular injections.

For permission to report this case it is a pleasure to record my thanks to Dr. F. C. Robbins, Director of Pediatrics, and Dr. F. A. Simeone, Director of Surgery. I wish to thank Dr. E. A. Mortimer, Jr., for his helpful criticism and advice.

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THE DIAGNOSIS AND TREATMENT OF HERMAPHRODITISM*

BY

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(RECEIVED FOR PUBLICATION OCTOBER 8, 1959)

Until recently the determination of the sex of an individual was mainly based upon the gonadal structure, and the sexual individuality identified with this finding. Accordingly a person having testes was a man and one having ovaries a woman. In the hermaphrodites certain anomalies inside the genital tract were considered more or less as anatomical variations from the normal without more profound changes in the sexual structure of the organism.

Clinical investigations into the various problems of hermaphroditism have, however, changed this picture completely and have shown how much more complicated these things are and how many different factors are working together to build up the harmonious sexual individuality of a human being. Today, in cases where the sex of the child is dubious, thorough investigations must be performed before any determinations as to the sex are made or any treatment can be instituted. The investigations should determine five different aspects of the organisms: (1) the genetic sex, (2) the gonadal sex, (3) the somatic sex—including the external and internal genitalia and the secondary sexual character, (4) the hormonal status, and (5) the psychic structure, including the rearing and gender role of the patient. Only then can a satisfactory decision be made.

The present paper is intended as a short introduction to some of the clinical aspects of hermaphroditism based on a personally known group of human hermaphrodites.

Investigation

In the years 1948-1959, 31 cases of hermaphrodites were investigated at the University Clinic of Paediatrics in Copenhagen. Fourteen of these were found to be *female* and 17 *male* pseudohermaphrodites. There were no true hermaphrodites, i.e. patients with both ovarian and testicular tissue inside the same organism.

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Liverpool in June, 1959.

Female Pseudohermaphrodites.

TABLE I
FEMALE PSEUDOHERMAPHRODITES

Adrenogenital syndrome	13
Origin unknown	1

All but one of the patients in the group of female hermaphrodites suffered from the adrenogenital syndrome. Nuclear sexing (Barr, 1955) showed female chromatin pattern. The clinical examination displayed more or less virilized external genitalia with a large phallus and some fusion of the labioscrotal folds (Fig. 1). A vagina and a uterus could be demonstrated either by inspection, endoscopy or radiography (Fig. 2). In three doubtful cases laparotomy was performed. The anatomy of the internal genital tract turned out to be of three different types. In the most common type—11 cases—the vagina and the uterus opened into the posterior urethra. In one case the vagina had a normal opening into the perineum and in another it was completely closed off from the urinary tract.

High 17-ketosteroid excretion in the urine gave the exact diagnosis with minimum 5 mg./24 hours in the newborn and maximum 12 mg./24 hours when the children reached the age of 1 year or more.

A high familial incidence in the group of adrenogenital syndrome was found in our investigation with three pairs of siblings, one pair being twin girls, the other two a boy and a girl. The two boys were also suffering from the adrenogenital syndrome but, not being pseudohermaphrodites, they are excluded from this group of *female* pseudohermaphrodites.

The last patient in the group did not suffer from the adrenogenital syndrome, the 17-ketosteroid excretion being 0·5 mg./24 hours. Nuclear sexing showed chromatin positive pattern indicating that genetically the child was female. The external genitalia were rather virilized (Fig. 3). Endoscopy

showed a vagina and a uterus. Gonads were not palpable. Laparotomy was unfortunately not performed, but would have been necessary in order to eliminate the possibility of true hermaphroditism. The history of the mother's pregnancy revealed no androgen treatment of any sort, as is sometimes the case in these patients (Wilkins, 1957). No reason for the virilism of this child could be demonstrated.

Male Pseudohermaphrodites.

TABLE 2
MALE PSEUDOHERMAPHRODITES

Female appearance	7
Male appearance	10

In the first group of male pseudohermaphrodites all seven patients were members of two families with 'testicular feminizing syndrome', with three in one family and four in the other. In six of the cases nuclear sexing was performed showing chromatin negative pattern. Gonadal biopsy showed testicular tissue as it is seen in cryptorchism. The external appearance, especially the external genitalia, were completely feminine (Figs. 4 and 5). A small vagina and no uterus was all that was found of internal genitalia.

The oldest of these patients, a 17-year-old 'girl', showed typical feminine development at puberty (Fig. 6) with normal breast development but with amenorrhoea as must be the case in a person lacking a uterus, and with the characteristic phenomenon seen in these patients, namely, lack of pubic hair.

The 10 patients belonging to the group *male* pseudohermaphrodites of *male* appearance were found to be a very heterogeneous group, being genetically males with chromatin negative pattern, having testes proved by biopsy but with ambiguous external genitalia and persistent Müllerian ducts of various sorts. Figs. 7 and 8 show such a patient, a boy with vulvular hypospadias and with both vagina and uterus.

In four cases a sudden strong virilism at puberty was the first sign which aroused the doubt about whether a correct decision of sex had been made at birth. The genitalia until then were of such a feminine character that neither midwife, family physician nor parents had had any suspicion of dealing with a hermaphrodite. Figs. 9-13 show one of these children, who had been followed up in our department from the age of 3 until the age of 14 years. The final examination was delayed because of disease in the family. Investigation at puberty (Figs. 12 and 13) proved the patient genetically to be a boy. The gonads were testes with no ovarian tissue and the hormonal status displayed an explosive hyperactive puberty with very high estrogens (>200 <400 Mouse/U./24 hours) and androgens (42%).

Finally the psychological investigation revealed both male and female elements in spite of the patient having been reared as a girl since birth.

Figs. 14-16 demonstrate the three other patients with female legal sex from birth, but with strong virilism near puberty. These difficult cases raise the important question of adequate approach to treatment, i.e. whether to change the sex, or remove the gonads. The problem will be discussed later in this paper.

Discussion

It is now possible, as a result of these detailed examinations of patients with ambiguous genitalia, to classify most hermaphrodites and to assemble them in different clinical groups.

The study of the chromatin pattern is an easy procedure: a buccal smear is enough for examination and, together with an analysis of the hormones in the urine, should always be undertaken, when doubt arises about the sex. Chromosomal counting, on the other hand, is still a rather complicated technique which only a few can master at present but in those cases where it can be done, the results are of great scientific and clinical value.

Gonadal biopsy as well as explorative laparotomy should be performed in almost all cases of pseudohermaphroditism except those with the adrenogenital syndrome, when other examinations have failed to give a clear answer. With the present state of paediatric surgery these procedures can safely be done in infancy. The increasing number of true hermaphrodites described in the literature demonstrates the importance of these explorations, especially with regard to gonadal biopsy, which should include incision throughout the whole length of each gonad found in the individual (Innes Williams, 1958).

The high familial incidence found in male and female hermaphrodites is well known (Morris, 1953; Holmer, quoted by Everse, 1958) and is illustrated in this material. In one of our two families with the testicular feminizing syndrome, where the parents were first cousins, no less than four out of eight children suffered from this syndrome (Fig. 17). The other four children were normal. In a branch of the same family another type of male pseudohermaphroditism was found (see Fig. 16).

Clinically two problems are met with in these patients: (1) Determination of sex at birth; (2) Decision regarding later medical and surgical treatment

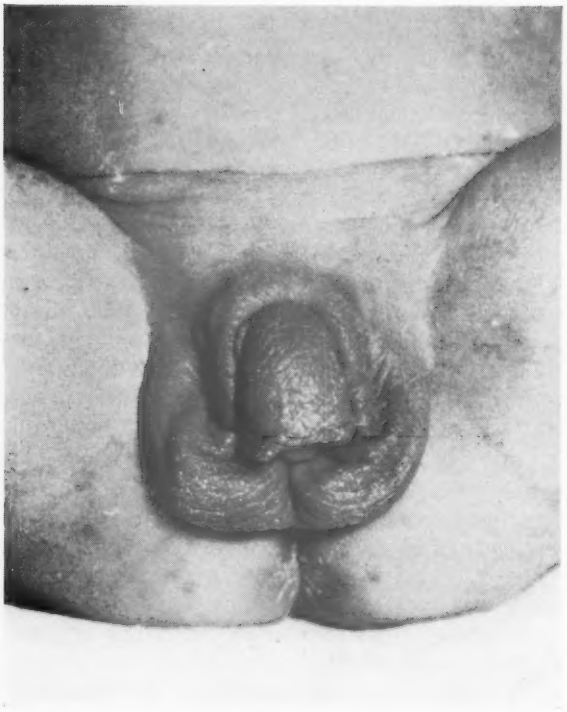


FIG. 1.

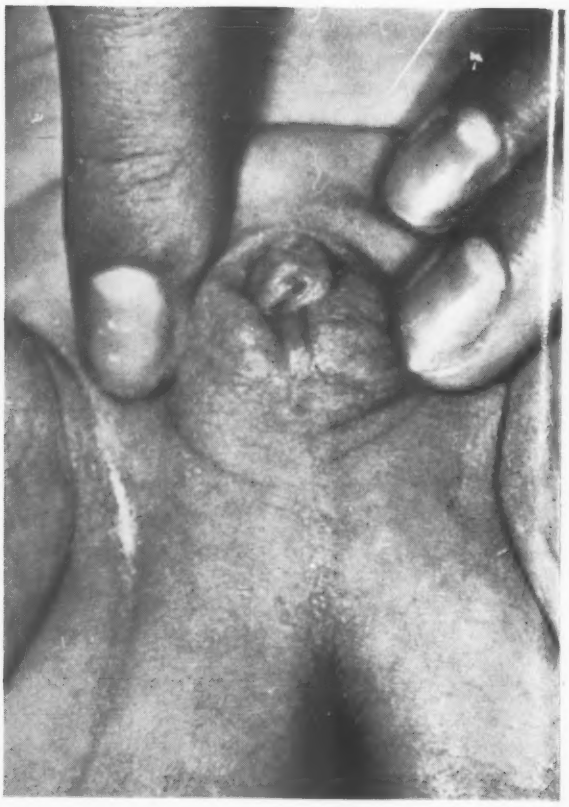


FIG. 3.

FIG. 2.

FIG. 1.—Adrenogenital syndrome.

FIG. 2.—Same patient, hysterosalpingography.

FIG. 3.—Girl with normal 17-ketosteroid excretion and virilized genitalia.

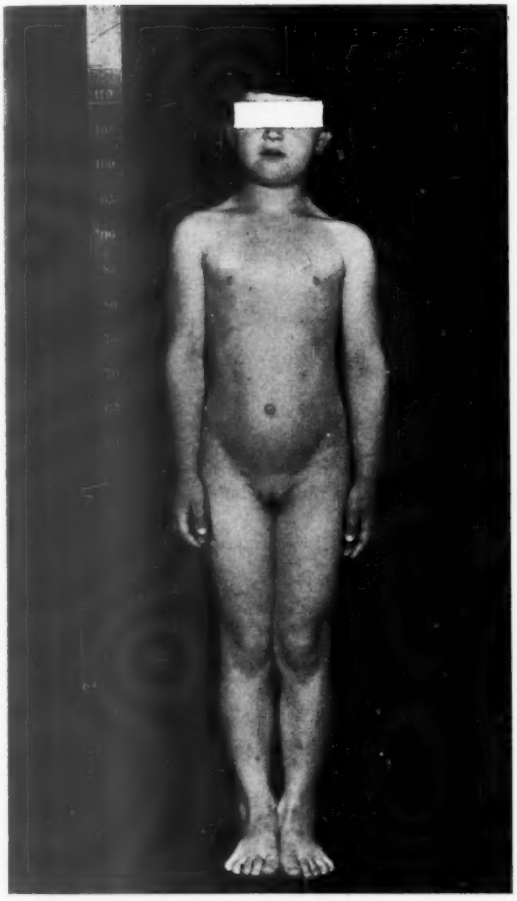


FIG. 4.

FIG. 5.

FIGS. 4 and 5.—Testicular feminizing syndrome. Appearance, including genitalia, completely feminine.

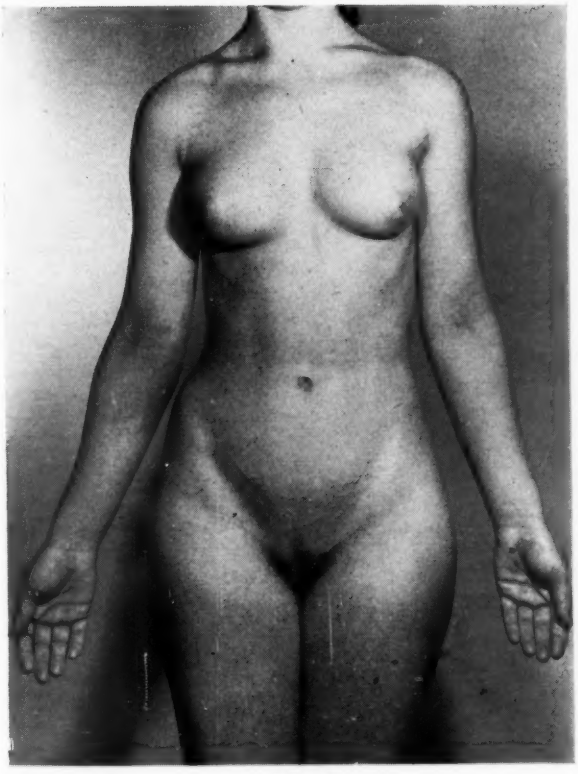
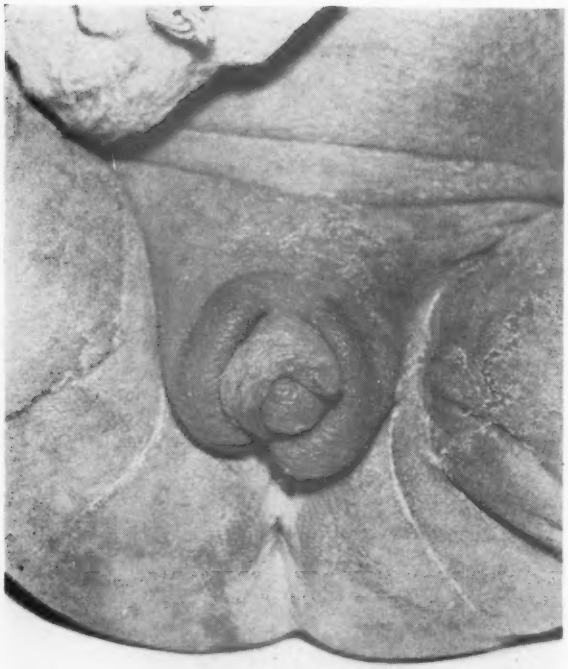
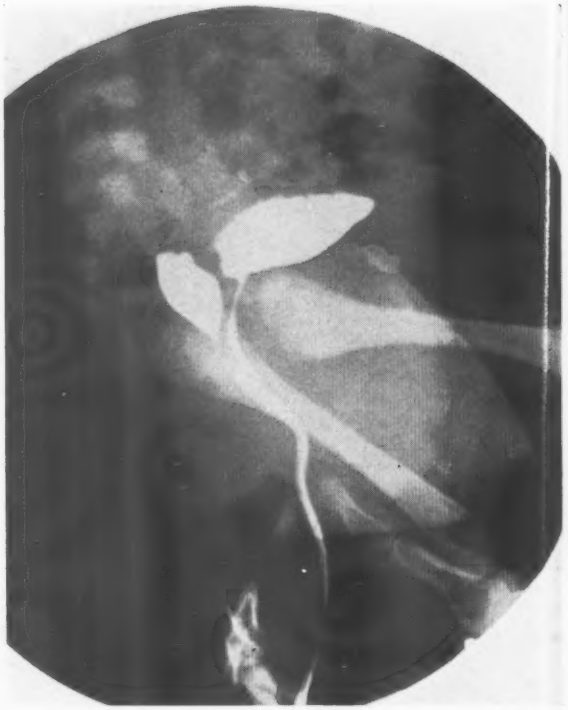


FIG. 6.

FIG. 6.—17-year-old patient suffering from the testicular feminizing syndrome. Feminine breast development but no pubic hair.





FIGS. 7 and 8.—Boy with vulvular hypospadia. Urethrography reveals both vagina and uterus.

FIG. 8

FIG. 9.

FIG. 10

FIGS. 9 and 10.—Male pseudohermaphrodite of feminine appearance.

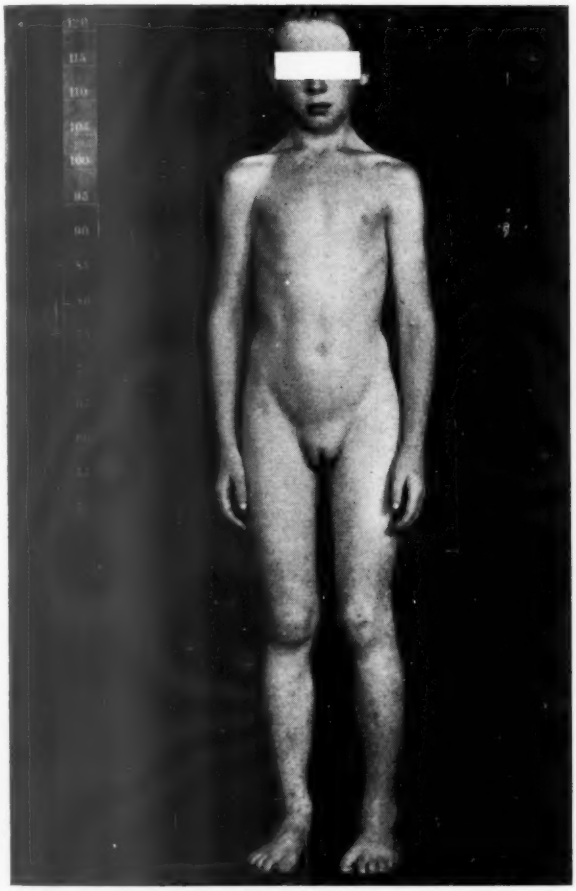


FIG. 11.

FIG. 12

FIG. 13.

FIGS. 11, 12 and 13.—Male pseudohermaphrodite of feminine appearance until puberty where strong virilism sets in (same patient as in Figs. 9 and 10.)

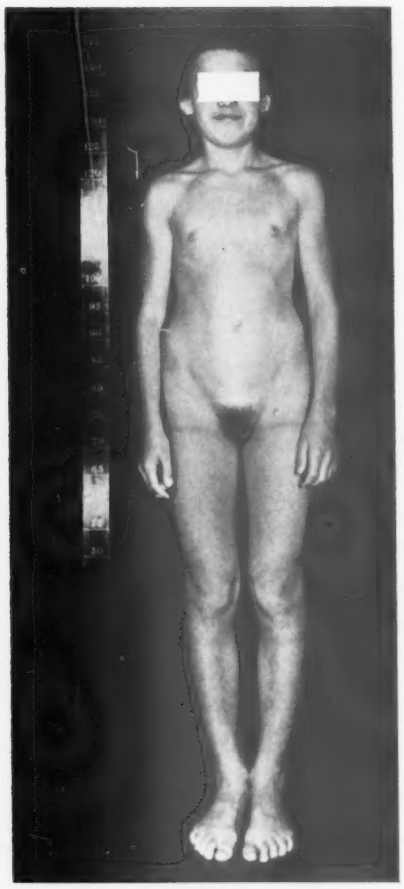


FIG. 14

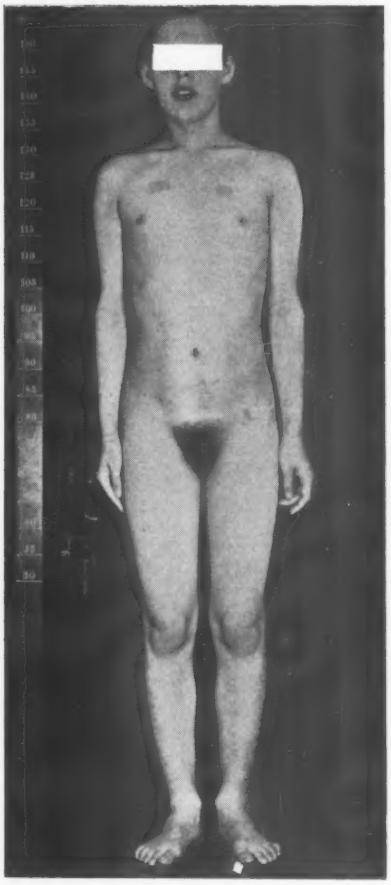


FIG. 15

FIG. 16

Figs. 14, 15 and 16.—All patients with female legal sex at birth but with strong virilism at puberty.

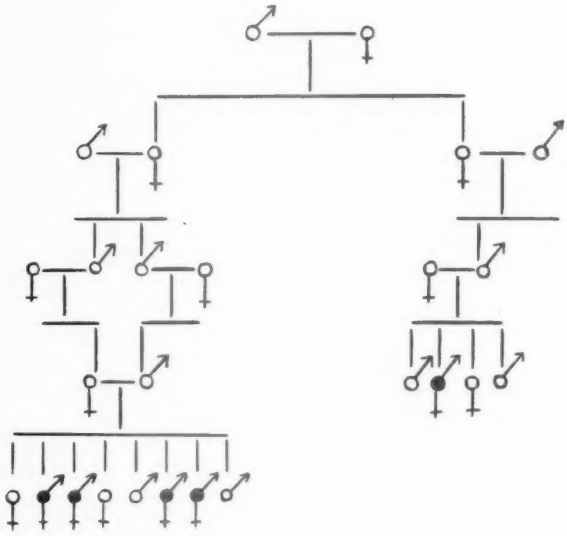


FIG. 17.—Familial incidence of pseudohermaphroditism.

FIG. 17.

when signs of abnormal development appear in later childhood.

Regarding sex determination, in many cases the decision regarding the sex of the patient can be based on the findings of the genetic, gonadal and somatic sex. On the other hand the general opinion seems to favour following the anatomy of the external genitalia. If these are mainly female, the child should be registered as a girl (Fig. 18) in spite of being genetically a boy and having testes. Such a patient is easier to adapt to the female role than to the male. But the decision must be made at birth or in the first months of life.

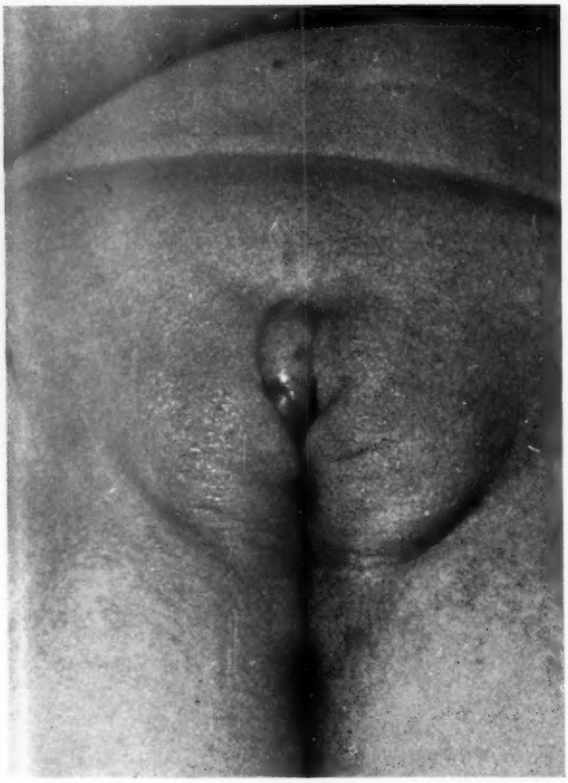


FIG. 18.—Child with mainly female external genitalia, genetically a boy with testes.

Regarding a decision on medical and surgical treatment in infancy and later childhood this will vary considerably from case to case and must depend on what kind of hermaphrodite it is and upon the age of the patient when seen.

Adrenogenital Syndrome. Seen at birth the right sex can be chosen in accordance with nuclear sexing and hormonal status. When cortisone treatment (Wilkins, 1957) is started and continued throughout life these girls will develop into normal women, will menstruate and can give birth to children.

Sooner or later corrective surgical procedures, comprising phallectomy and closure of the abnormal opening of the vagina into the urethra with vulvuloplasty, should be undertaken. Jones and Scott, (1958) recommend the age of 1 year as being the best age for these procedures.

In the present material six phallectomies were done, the age of the children varying from 1 to 5 years. In one case it was done already in early infancy on account of emigration.

The question of the necessity of phallectomy with its possible injuring sequelae has been discussed a great deal. It is, however, the majority opinion that, as long as the phallus does not diminish in size during cortisone treatment, the operation should be undertaken at least in those cases where the phallus is of considerable size. According to Money, Hampson and Hampson (1955) this procedure does not interfere with the normal mature sexual life.

Adrenogenital syndrome in older female children reared as boys but suddenly found to be girls brings up the question of changing the sex. This is a difficult problem, and the general opinion seems to be crystallizing to the view that, after the age of 1 year, change of sex in this condition as in most other types of hermaphroditism is psychologically hazardous and should not be undertaken (Money *et al.*, 1955).

In the present investigation only one patient, less than 3 years of age, was changed from a boy to a girl and cortisone treatment instituted. This happened five years ago, but overwhelming psychic conflicts are still to be found both in the child and the parents.

In our opinion, patients with the adrenogenital syndrome, being girls from a genetic and gonad standpoint, but reared as boys, should be left as males, have the hypospadias corrected and the ovaries removed. They then feel and act like men and their gender role will clearly be male when they mature.

A patient in the present material demonstrates what can happen to the clinical picture years after puberty, if the gonads have not been removed:

L.C. was reared as a girl until 1935 at the age of 9 years the sex was changed on account of virilization with simultaneous surgical correction of the hypospadias. At the age of 30 years, when the patient was living a well adjusted life as a married man, there was a sudden development of breasts, which were removed. A year later the patient menstruated heavily from the hidden

vagina and uterus. Laparotomy was performed, a fibroma in the uterus was found and hysterectomy was carried out.

Male Pseudohermaphrodites with Female Appearance. This group includes patients with the testicular feminizing syndrome.

In childhood they are occasionally discovered during herniotomies, when a gonad is found and turns out to be a testis. In each of our two families one patient was primarily discovered this way, giving rise to a thorough examination of the others.

In these very female individuals, in whom it is known that their gender role will be that of a woman in spite of having testes and genetically being males the question arises whether the gonads should be removed or not.

This may be difficult to answer. Left in the groin, as some propose (Wilkins, 1957) they grow, become large and give an unpleasant feeling. If removed, puberty does not develop. Placed within the abdomen there will be a 10% risk for malignant degeneration (Morris, 1953). Jones and Scott (1958) advise that the gonads should be left untouched until the early twenties and then removed.

In most of our cases the gonads have been left or, during herniotomy, replaced in the abdomen and in only two cases have they been removed. The rest of our patients have not yet reached the age of 20 and the decision whether to remove the gonads or not has, accordingly, not been made yet.

Male Pseudohermaphrodites with Male Appearance. In this group the real problems are met at puberty when sudden virilization appears in children reared as girls. No simple answer can be given to the question how best to handle these patients, and many individual factors will affect the final decision. In most cases it is probably advisable to remove the gonads and make corrective plastic procedures and thus let them remain female individuals. This has been the case in three of our four patients at the ages of 13-14 and 15 years.

On the other hand the possibility of changing a girl to a boy at the age of more than 1 year cannot be ruled out. In one of our cases the child, who was reared as a girl but genetically was a boy with testes, virilized at the age of 13 and insisted upon being changed into a boy (Fig. 15). This demand was met, but unfortunately the patient left the country so that no follow-up has been possible.

Conclusion

Patients with ambiguous genitalia at birth must immediately be carefully examined before the legal sex is decided, and in most cases both gonadal biopsy and explorative laparotomy will be a necessary part of the examination with the exception of patients suffering from the adrenogenital syndrome. The choice of sex depends more than anything else on the structure of the external genitalia.

Seen later in childhood, roughly speaking after 1 year of age, all the same examinations must be performed, but from this time it is advisable to leave the patient with the legal sex given at birth. Accordingly, corrective surgical procedures should be undertaken including excision of contradictory sex structures and in some cases removal of the gonads. The change of sex in later childhood will only rarely present a satisfactory solution of the problem.

Summary

The modern concepts of hermaphroditism are discussed based upon 31 cases of pseudohermaphroditism of which 14 were female and 17 male pseudohermaphrodites. The diagnosis and treatment in each group of patients are discussed.

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BRITISH PAEDIATRIC ASSOCIATION

Proceedings of the Thirty-first Annual General Meeting

The Annual Meeting of the British Paediatric Association was held at the Royal Hotel, Scarborough, from May 4 to 7, 1960.

BUSINESS PROCEEDINGS. Dr. Reginald Lightwood took the Chair as President, and the following members were present:

A. G. V. Aldridge, E. C. Allibone, H. Angelman, I. M. Anderson, J. Apley, Cecile Asher, R. Astley, M. W. Arthurton, Margaret Baber, A. D. Barlow, R. E. Bonham Carter, J. A. Black, A. C. Blandy, M. Bodian, J. V. Braithwaite, T. A. Brand, P. T. Bray, G. Brewis, F. S. W. Brimblecombe, R. W. Brookfield, D. Browne, N. R. Butler, W. H. Cant, I. A. B. Cathie, N. S. Clark, E. C. R. Couper, J. O. Craig, J. Craig, W. S. Craig, Mildred Creak, J. Crooks, K. W. Cross, G. Davison, C. E. Dent, E. F. Dott, D. M. Douglas, A. C. Doyne-Bell, Margaret Eastwood, J. L. Emery, J. W. Farquhar, H. V. L. Finlay, O. D. Fisher, J. O. Forfar, Isabella Forshall, A. White-Franklin, D. M. T. Gairdner, W. F. Gaisford, B. Gans, J. M. Garvie, R. R. Gordon, I. H. Gossett, E. W. Hart, C. C. Harvey, J. D. Hay, W. Henderson, J. B. Heycock, D. V. Hubble, A. Holzel, R. S. Illingworth, R. J. Isaac, N. M. Jacoby, Ursula James, R. T. Jenkins, H. Jolly, H. Everley Jones, F. F. Kane, A. C. Kendall, C. W. Kesson, A. C. Kirby, B. M. Laurance, D. N. Lawson, R. C. Lightwood, J. Lorber, R. A. McCance, Anne McCandless, P. MacArthur, J. C. Macaulay, A. M. MacDonald, Agnes R. MacGregor, M. MacGregor, Helen M. M. Mackay, T. Mann, W. J. Matheson, R. M. Mayon-White, R. A. Miller, R. G. Mitchell, D. Morris, F. W. Nash, A. V. Neale, G. Neligan, C. Newman, T. C. Noble, A. P. Norman, J. N. O'Reilly, A. P. M. Page, W. W. Payne, M. G. Philpott, J. D. Pickup, L. J. Prosser, R. J. Pugh, P. P. Rickham, E. G. G. Roberts, T. S. Rodgers, K. B. Rogers, J. Rubie, J. Sakula, B. E. Schlesinger, L. G. Scott, R. A. Shanks, W. Sheldon, Victoria Smallpeice, W. C. Smallwood, J. M. Smellie, J. Forest Smith, R. E. Smith, A. L. Speirs, J. M. Stansfield, T. Stapleton, R. E. Steen, D. G. H. Stone, W. P. Sweetnam, P. N. Swift, James Thomson, John Thomson, M. L. Thomson, R. McL. Todd, C. W. Vining, D. G. Vulliamy, W. Walker, D. H. Wallace, H. R. E. Wallis, C. Warren, A. G. Watkins, D. J. Waterston, S. D. V. Weller, I. G. Wickes, R. Wigglesworth, D. A. J. Williamson, B. D. R. Wilson, O. H. Wolff, T. Wright, Winifred Young, S. Yudkin, R. B. Zachary.

Professor J. Lind, Stockholm (Windermere Lecturer) and Mr. G. J. Piller were the guests of the Association.

The following were present as guests of members of the Association:

A. W. Abramson, E. Back (Jamaica), J. P. Bound, E. T. Bowen (U.S.A.), J. E. Bowman (U.S.A.), T. Bird, R. J. K. Brown, M. F. G. Buchanan, E. A. J. Byrne, I. J. Carré, R. A. Chenoweth (Australia), Vernon Collins (Australia), J. G. Dathan, D. Danks (Australia), W. Dickson, Margaret Egan, C. G. Fagg, C. V. Feldman, C. M. B. Field, H. J. W. Fisher, M. S. Fraser, J. G. H. Frew, E. Frisell (Sweden), H. McC. Giles, R. Godfrey (Australia), E. Goldblatt (South Africa), R. A. Goodell (U.S.A.), J. L. Greaves, Mary Hallowell, O. K. Harlem (Norway), L. A. Hawkins, G. Helderweirt (Belgium), G. Hesling, D. Hilson, C. Hooft (Belgium), K. S. Holt, T. T. S. Ingram, A. D. M. Jackson, R. H. Jackson, S. Keidan, K. R. Llewellin, June Lloyd, J. Luder, S. J. R. Macoun, R. I. Mackay, Muriel McLean, B. McNicholl, M. Brenda Morris, P. D. Moss, J. S. Oldham, M. Pacht (Israel), K. R. Parker (U.S.A.), B. W. Powell, R. Prosser, J. P. Quinton, J. P. R. Rees, T. J. Rendle-Short, I. D. Riley, A. P. Roberts, T. R. Savage, T. Morton Stewart, Dorothy Taylor, D. C. Thursby-Pelham, J. J. Tillie, W. M. L. Turner, H. Vertruyen (Belgium), O. C. Ward, B. W. Webb, R. G. Welch, R. H. R. White, B. Wolman, R. J. Young.

The Annual General Meeting was held on May 5, 1960.

The Minutes of the last meeting, which had been published in the *Archives of Disease in Childhood* were received and, subject to a minor correction, approved.

ELECTION OF OFFICERS. The following were elected:

PRESIDENT: Professor A. V. Neale
PRESIDENT-ELECT: Professor A. A. Moncrieff
HONORARY TREASURER: Professor A. G. Watkins
HONORARY SECRETARY: Dr. E. W. Hart

EXECUTIVE COMMITTEE, 1960-63:
Dr. W. A. B. Campbell, Dr. W. Henderson, Dr. G. M. Komrower, Mr. R. B. Zachary.

ELECTION OF MEMBERS. The following were elected:

HONORARY MEMBER

Dr. C. T. Potter

ORDINARY MEMBERS

A. W. Abramson (Ayrshire), Enid I. M. Addenbrooke (North Gloucestershire), D. W. Beynon (Bournemouth), J. P. Bound (Blackpool), R. J. K. Brown (London), M. F. G. Buchanan (Leeds), J. H. Burkinshaw (London), E. A. J. Byrne (Lancaster), I. J. Carré (Belfast), H. M. T. Coles (London), D. G. Cottom (London), A. A. Cunningham (Kingston, Surrey), J. G. Dathan (Stoke-on-Trent), W. Dickson (Bolton), Margaret Egan (Manchester), C. G. Fagg (Luton), G. V. Feldman (Manchester), C. M. B. Field (Belfast), H. J. W. Fisher (Hereford), R. M. Forrester (Wigan), M. S. Fraser (Aberdeen), Muriel J. L. Frazer (Belfast), J. G. H. Frew (Birmingham), A. A. H. Gailey (Belfast), H. McC. Giles (Birmingham), J. L. Greaves (Tees-side), A. G. Hesling (Preston), D. Hilson (Ashton), E. Hinden (London), K. S. Holt (Sheffield), T. T. S. Ingram (Edinburgh), A. D. M. Jackson (London), R. H. Jackson (Newcastle-upon-Tyne), S. E. Keidan (Liverpool), K. R. Llewellin (Clatterbridge), J. Luder (Watford), S. J. R. Macoun (Guildford), R. I. Mackay (Salford), B. McNicholl (Galway), Muriel M. McLean (Clwyd and Deeside), Zina E. Moncrieff (London), M. Brenda Morris (Barrow), P. D. Moss (Blackburn), F. W. Nash (Merthyr), J. S. Oldham (Birmingham), B. W. Powell (Peterborough), J. F. P. Quinton (Norwich), J. P. R. Rees (Dublin), T. J. Rendle-Short (Sheffield), I. D. Riley (Glasgow), A. P. Roberts (Dewsbury), T. R. Savage (Romford), D. C. Thursby-Pelham (Stoke-on-Trent), J. J. Tillie (Tees-side), W. M. L. Turner (Burnley), O. C. Ward (Dublin), B. W. Webb (Taunton), R. G. Welch (Hartlepool), B. Wolman (Bury), R. J. Young (Londonderry).

The Treasurer's report and statement of accounts for the year 1959-60 were received and adopted and the auditors were re-appointed for the coming year.

The report of the Executive Committee was received and is printed below.

The recommendation of the Executive Committee 'That the title of the Executive Committee should be changed to the Council of the British Paediatric Association' was approved.

The recommendation of the Executive Committee that Rule 2 should be altered to 'It shall consist of Ordinary Members, Honorary Members and Corresponding Members. Ordinary Members shall be actively engaged in the practice or teaching of paediatrics or in paediatric research. In addition individuals who have contributed to the advancement of paediatrics in the allied specialties may be nominated for Ordinary Membership, but election of these shall be on a restricted basis and maintain a balance between the specialties', was approved.

The President reported that Messrs. Cow and Gate had donated £200 as a grant in aid to assist members in travel on the Association's business or other travel approved by the Association. The President also reported the generous offer by Messrs. H. J. Heinz Company Ltd. of £2,500 per annum for seven years in the first instance to endow Commonwealth travelling fellowships. These offers were accepted with acclaim.

Professor A. V. Neale, on behalf of the Association, thanked the President for the part which he had played in these negotiations.

Report of the Executive Committee 1959-60

OBITUARY. The Association has suffered the loss of one honorary member, Sir Robert Hutchison, an original member and former President, and also the loss of two corresponding members, Professor Bronson Crothers and Dr. J. L. Gamble.

EXECUTIVE COMMITTEE

The membership of the Executive Committee during the year 1959-60 has been: Dr. J. Apley, Dr. I. A. B. Cathie, Dr. P. R. Evans, Dr. J. Forest Smith, Miss I. Forshall, Dr. A. White Franklin, Dr. E. W. Hart, Professor D. V. Hubble, Dr. F. F. Kane, Dr. R. C. Lightwood, Dr. P. MacArthur, Dr. M. MacGregor, Professor A. V. Neale, Dr. L. G. Scott, Dr. Victoria Smallpeice, Dr. J. P. M. Tizard, Professor A. G. Watkins.

The following are invited to attend as observers: Sir Wilfrid Sheldon (Advisor in Child Health to the Ministry of Health); Dr. C. Asher (Ministry of Education); Dr. J. C. R. Buchanan (Colonial Office); Dr. D. Taylor (Ministry of Health).

The Committee met in November, 1959 and February, 1960 and will meet again on May 4th, 1960. In addition to receiving reports from sub-committees (see below) the following matters were among the more important to be considered:

The Executive noted with great pleasure the distinctions conferred on Sir Wilfrid Sheldon, K.C.V.O., and Dr. Dorothy Taylor, C.B.E.

1. MEDICAL CARE OF ADOLESCENTS. (D. V. Hubble, R. R. Gordon, R. C. Mac Keith, Victoria Smallpeice and R. E. Smith.) The report of this sub-committee was published in *The Lancet*.

2. CHILDREN IN ADULT WARDS. Representation was made to the Faculty of Ophthalmologists concerning the nursing of children in adult ophthalmic wards. This was considered by the Council of the Faculty and a favourable reply was received, stating

that the views of the Platt Committee had been noted and accepted.

3. APPOINTMENT OF PHYSICIANS TO PRACTISE PAEDIATRICS. A survey of the number of general physicians having care of children's wards was carried out. The number was not large. In one recent example when such an advertisement was published, the Association had investigated through one of the members and had been satisfied that this was the only practical solution in this case.

4. ADMISSION OF SPECIALISTS TO MEMBERSHIP OF THE ASSOCIATION. The Executive Committee had considered the election of specialists to ordinary membership. A proposal to alter Rule 2 of The Association is to be submitted at the Annual Meeting to try and establish the criteria on which such elections should be made.

5. HOME CARE SCHEMES. A request was received from the Central Consultants and Specialists Committee seeking the views of the Association on the value of Home Care Schemes for the treatment of sick children. The Association stated that it was in favour of such schemes in general. The Executive Committee felt that it was necessary to clarify their policy with regard to such schemes. A sub-committee was set up (M. MacGregor, J. Apley, F. S. W. Brimblecombe, D. Gairdner and L. G. Scott) and has submitted two interim reports to the Executive Committee and is at present reframing this report in the light of comments which have been made.

6. CONSULTANT PAEDIATRICIAN APPOINTMENTS.

7. THE PROBLEMS OF THE REGIONAL PAEDIATRICIAN.

8. THE JOINT WORKING PARTY ON THE STAFFING STRUCTURE IN THE HOSPITAL SERVICE.

Three closely allied problems have arisen during the past year. Last year the report of the Executive Committee indicated a keen interest in the future appointments of paediatricians and the need to train individuals for these appointments. The discussion at the Annual meeting, 1959, on 'The Problems of the Regional Paediatrician' raised further points. The Joint Working Party on the Medical Staffing Structure in the Hospital Service invited the Association to submit a memorandum on the paediatric services. The President set up an ad hoc Committee (R. C. Lightwood, P. R. Evans, E. W. Hart, D. V. Hubble, M. MacGregor, L. G. Scott and A. G. Watkins) which prepared a memorandum. This was submitted to the Joint Working Party which later requested oral evidence on April 6. The Association was represented by E. W. Hart, P. MacArthur, M. MacGregor and A. G. Watkins.

The Executive Committee considered these three topics at the November meeting and initiated a survey of all paediatricians to obtain information about the present structure of the paediatric services.

The questionnaire was sent to 242 individuals having paediatric sessions and was completed by 221. The replies are still under analysis and have given a picture of the paediatric staffing of the country and have emphasized the position of the paediatrician in relation to the care of the newborn infant, the local Health Authority clinics and infectious diseases units, and have given facts concerning the difficulties in obtaining junior staff, cover for paediatricians on leave and prospects for senior registrars.

A preliminary report will be given at the Annual Meeting at Scarborough.

9. COMMONWEALTH TRAVEL FELLOWSHIPS. As reported last year, negotiations have been undertaken to raise money to assist Commonwealth paediatricians to visit this country each year, either at a time which would permit attendance at the Annual Meeting or for periods of post-graduate study. Negotiations have reached a hopeful stage, and it is hoped that a further report will soon be available.

10. COW AND GATE GRANT IN AID. Messrs. Cow and Gate have generously donated the sum of £200 for one year in the first instance. This money is to be used to assist members in meeting the expenses of duties approved by the Association.

11. VISIT TO SWEDEN 1960. At the February meeting the Executive Committee conducted a ballot to select the names of the party to visit Sweden in September, 1960 at the invitation of the Swedish Paediatric Association.

12. LIAISON WITH THE BRITISH MEDICAL ASSOCIATION. In response to representation from the Association a letter was received from the Secretary of the B.M.A. stating that the Council of the B.M.A. would bear in mind the P.B.A.'s request for consultation on paediatric problems which the B.M.A. may consider in the future, but that it could not commit itself always to do so.

13. CASULTY SERVICES AND UNITS. The Executive Committee wrote to the President of the Royal College of Surgeons requesting that full consideration should be given to the proper care of infants and young children when the Royal College of Surgeons met to consider the future planning of Casualty Services and Units. This problem remains under further review.

14. ANNUAL MEETING, 1961. The joint meeting with the Canadian Paediatric Society

is planned for the last week in June, 1961 in Cambridge.

15. INTERNATIONAL PAEDIATRIC ASSOCIATION. A request was received from the International Paediatric Association to send a representative to Zurich to discuss 'Some selective measures which will increase definitely the standard of Paediatric education'. This was declined as it was considered that the W.H.O. inquiry had not been fruitful owing to its inherent difficulty and the unsatisfactory nature of the questionnaire.

16. OTHER TOPICS. Other topics which have been discussed are: Paediatric Education in Europe; The Fountain Hospital; The International Paediatric Association; a proposed Institute of Child Care, and arrangements for the annual meeting.

STANDING COMMITTEES

CHILD PSYCHOLOGY: J. Apley, D. MacCarthy, Mildred Creak, R. M. Mayon-White, D. V. Hubble, A. A. Moncrieff, R. C. Mac Keith, C. T. Potter.

The sub-committee has reported to the Executive Committee at each meeting. The Standing Committee is discussing liaison with the Mental Deficiency Section of the Royal Medico-Psychological Society. The Standing Committee has recommended a change in its title to 'Standing Committee on Mental Health' and this has been approved.

NURSING: Mildred Creak, R. S. Illingworth, Sir Wilfrid Sheldon, D. J. Waterston, A. G. Watkins.

The Committee has had discussions with the Association of British Paediatric Nurses and has furnished an interim report. Further discussions are to be held.

TROPICAL PAEDIATRICS: R. W. B. Ellis, R. Lightwood, A. A. Moncrieff, M. MacGregor, A. G. Watkins, Cicily Williams.

No report.

JOINT COMMITTEE WITH R.C.O.G.: P. R. Evans, J. H. Hutchison, R. Lightwood, F. J. W. Miller, A. A. Moncrieff.

Has not met since formation in 1958.

JAMES SPENCE MEDAL: P. R. Evans, C. G. Parsons, R. A. McCance, F. J. W. Miller, The Secretary (ex officio).

The Committee has met and has prepared a report.

REPRESENTATIVES:

National Association for mental health: J. Apley

U.K. Committee for Poliomyelitis: E. W. Hart.

Maternity and Midwifery Committee of the Ministry of Health: J. Forest Smith.

Joint Tuberculosis Council: W. F. Gaisford.

Standing Maternity Hospital Report Committee of R.C.O.G.: A. A. Moncrieff.

Medical Advisory Committee of Nursery School Association: L. G. Scott.

Leonard Parsons Memorial Committee: S. Graham.

National Association for Maternity and Child Welfare: A. White Franklin.

Editorial Committee, *Archives of Disease in Childhood:* see list in *Archives.*

AD HOC COMMITTEES

ACCIDENTS IN CHILDHOOD. An ad hoc sub committee (J. O. Craig, V. Smallpeice, and S. Yudkin) was set up to consider the extent to which the Association should participate in consideration of this problem. After receiving the report of the sub-committee at the February meeting, it was decided to set up a standing Sub-Committee on Accidents in Childhood to keep the problem under constant review. The Sub-Committee includes J. O. Craig, Isabella Forshall, R. C. Mac Keith, Victoria Smallpeice, R. B. Zachary and S. Yudkin.

MEDICAL SERVICES REVIEW COMMITTEE (PORRITT COMMITTEE). The Porritt Committee requested the following memoranda which were submitted:

(*a*) Psychiatric Services; (*b*) Welfare of Children in Hospital; (*c*) The Medical Care of the Adolescent; (*d*) Report on Hospital Accommodation. An invitation was received from the Sub-Committee on Maternity and Child Health Services of the Medical Services Review Committee, to nominate a paediatrician to join the Sub-Committee. Professor W. S. Craig was invited to serve as our representative.

COMPOSITION OF MILK (COOK COMMITTEE): W. A. B. Campbell, I. A. B. Cathie, E. W. Hart, J. Thompson. Oral evidence was given by I. A. B. Cathie.

ARTIFICIAL INSEMINATION: W. S. Graig, E. W. Hart, A. P. Norman, C. O. Carter (co-opted). The Home Office Departmental Committee on Artificial Insemination (Feversham Committee) asked the Association to give oral evidence. W. S. Craig and E. W. Hart represented the Association.

INFECTIOUS DISEASES HOSPITALS: R. H. Dobbs, F. F. Kane, M. MacGregor and Dorothy Taylor. A questionnaire has been circulated and is under analysis.

Surveys

HYPERCALCAEMIA AND RICKETS. The survey continues and has been extended in scope to include cases of rickets up to the age of 5 years.

RIBOFLAVIN DEFICIENCY: No cases were reported.

NEED FOR A PAEDIATRIC ABSTRACTING SERVICE: This survey was undertaken at the request of the Editorial Committee of the *Archives of Disease in Childhood*, and the following replies were received:

(*a*) Do you use an abstracting service today?	Yes 86	No 36
(*b*) Do you feel the need of a paediatric abstracting service?	Yes 52	No 70

Notices

Tenth International Congress of Paediatrics.

The Congress will be held in Lisbon from September 9-15, 1962.

The President will be Professor C. Salazar de Souza, and the address of the Secretariat of the Congress is:

Clinica Paediatrica Universitaria,
Hospital de Santa Maria,
Avenida 28 de Maio,
Lisbon 4.

Registration fees: Active members 1000 Escudos. Associate members 600 Escudos.

Registration period, August 1, 1961 to January 31, 1962.

If any members wish to take their families by caravan or to camp, they should write to:

Clube de Campismo de Lisboa,
Rua de Misericordia, 137-20,
Lisbos,
Portugal.

where they will obtain all the necessary information.

SCIENTIFIC SESSIONS

J. O. CRAIG (Glasgow). 'Body Build in Childhood.' The measurement, tabulation and phenotyping of 3,900 Glasgow children by Parnell's method were described. 'Hermaphrodite' tables were used, so development of one sex could only be considered relative to the other. Boys are more muscular and less fat even at 5 years, the youngest group studied. Girls seem to show a boyish growth trend around 9 years. Children from good homes are more fat, more linear and less muscular than children from poor homes at all ages studied. The consistency of the findings suggests the method is valid in childhood, and can supply a somatic background to development and disease.

JAMES CROOKS (London). 'Posterior Choanal Atresia'. Bilateral posterior choanal atresia may be the cause of death in the newly born. Such a baby has so strong an instinct to nose breathe that he fails to learn the trick of mouth breathing and may suffocate to death within a day or two of birth. In the past probably such babies frequently died without the cause being recognized. This is less likely nowadays and recently on two occasions life has been saved by surgically removing the obstructing bone and membrane as an emergency measure within a day or two of birth. This, not tracheostomy or intubation, is the correct procedure.

J. APLEY (Bristol). 'Primary myocardial disease in infancy: clinical aspects.' In 24 infants (with autopsy in 20 fatal cases) the diagnoses were as follows: Glycogen storage disease of heart, one; aberrant left coronary artery, four; myocarditis, five; Endocardial fibroelastosis, 14.

Primary myocardial disease is not a pathological entity, but a clinical group of disorders with some features in common. These are summarized and illustrated and differential diagnosis within the group is discussed. The importance of diagnosis is stressed, because in some types of primary myocardial disease treatment may be life-saving. Some possible approaches to research on diagnostic methods and on aetiology are suggested.

T. J. RENDLE-SHORT (Sheffield). 'A development test based on the time taken to establish a conditioned reflex.' To be published in full.

IAN M. ANDERSON (London). 'Total Pulmonary Anomalous Venous Drainage.' The various types of total pulmonary anomalous venous drainage were described and 10 cases of this condition were recorded. The clinical features of the condition were discussed and also the various ancillary methods of diagnosis such as electrocardiography, radiology, angiocardiography and cardiac catheterization. The feasibility and importance of early recognition was emphasized with particular reference to the possibility of surgical correction with the aid of modern methods of open heart surgery.

R. H. R. WHITE (London). 'A comparative study of serum transaminase levels and liver biopsies.' Serum transaminase levels were estimated on capillary blood, by King's (1958) method, in 38 children from whom liver biopsies were obtained by either needle or surgical technique. The normal range is 10-110 μ. moles pyruvate/100 ml. serum/hour. Normal levels were found in polycystic disease and storage disorders, and normal or moderately elevated levels in cirrhosis. In five out of nine infants with giant-cell hepatitis SGOT levels were higher than 320 and SGPT levels higher than 500 μ. moles, while in all nine cases the GOT/GPT ratios were $< 1{\cdot}0$. In biliary atresia less elevated levels were found and the GOT/GPT ratios were $> 1{\cdot}0$ in five out of seven cases. While thus affording some guidance in obstructive jaundice, transaminase levels are not always sufficiently diagnostic to replace liver biopsy.

MARY HALLOWELL (Birmingham). 'Duodeno-jejunal biopsies in steatorrhoea.' The results of 40 duodeno-jejunal biopsies in children were reported. Twenty-nine of these children suffered from coeliac disease already established by other criteria and in all except one the

characteristic coeliac appearance of the small intestine mucosa was demonstrated. Eleven other children had a normal mucosa. Six of them did not have steatorrhoea at the time of biopsy, but the remaining five children had steatorrhoea. Of these five children one was a case of bile-salt deficiency, the second had no beta-lipoprotein in her serum and in the other three no cause was found for the steatorrhoea.

R. B. ZACHARY (Sheffield). 'Surgical aspects of a Controlled Series of Untreated Cases of Hydrocephalus, and those Treated with a Spitz-Holter Valve.' This paper reviews the failures in the treated group in order to assess which failures were attributable to remediable technical errors and which were a risk inherent in the method. The chief complication was thrombosis of the jugular vein beyond the lower end of the jugular catheter. This may be due to the insertion of too short a length of tubing into the jugular vein, or to the gradual elevation of the lower tip of the catheter due to growth of the child. The change of length in the superior vena cava, the innominate vein and the jugular vein with growth during the first few years of life is important, and must be allowed for either at the original operation or by a revision before thrombosis occurs.

A. P. NORMAN (London). 'Perceptive Deafness and Hyperbilirubinaemia.' Between the dates of May, 1953 and February, 1956, at Queen Charlotte's Maternity Hospital, 63 infants were born, in whom the total bile pigments reached a level of 20 mg./100 ml. Three of these cases have died and 14 could not be traced or failed to cooperate. Three more have not yet been investigated. In five cases audiometry was not carried out but normal hearing has been confirmed by other means. In 38 cases, audiometry was carried out: of these, three showed some hearing loss not perceptive and not associated with hyperbilirubinaemia. Five children showed perceptive high tone deafness: three of these were known to have cerebral palsy resulting from kernikterus due to rhesus incompatibility. Two were not previously known to be deaf: of these one had been affected by A.O. blood group incompatibility and the other was a premature baby with no known blood incompatibility. The maximum bilirubin concentration reached in these cases ranged from 34 mg./100 ml. in one case, to 20 mg./100 ml. in the case of the premature baby who showed no evidence of immunization. The findings of perceptive hearing loss in these cases suggests that the maximum bilirubin concentration should be kept somewhat lower than is sometimes advocated. These findings also suggest that perceptive deafness may complicate hyperbilirubinaemia without overt signs of kernikterus more often than is realized.

JUNE LLOYD (Birmingham). 'Observations on Primary Hyperlipaemia.' In a patient with primary hypercholesterolaemia treatment with a diet rich in unsaturated fat was successful in lowering serum lipids and improving the clinical condition. In contrast, two patients with idiopathic (neutral fat) hyperlipaemia showed clinical and biochemical improvement on a low-fat diet, whereas an unsaturated-fat diet was ineffective. Levels of alpha-lipoprotein were found to be low in idiopathic hyperlipaemia and the significance of this finding in relation to aetiology was discussed.

M. S. FRASER (Aberdeen). 'The Measurement of Children's Motor Ability.' Motor performance tests yielding numerical results, make possible the objective assessment of bodily abilities and should find various uses in paediatric research. This 'neurometric' approach is illustrated by methods employed in a follow-up study (*J. Obstet. Gynaec. Brit. Emp.*, 1959, **66**, 748) of 150 children who were asphyxiated at birth and of their rigorously matched controls. At 7-13 years of age, no convincing reduction of manual dexterity was observed, although speed, strength and precision were separately measured. Subclinical impairment of locomotor coordination was detected by Heath's rail-walking test.

WINDERMERE LECTURE. Professor J. Lind (Stockholm) delivered the Windermere Lecture entitled 'Aspects of the functional adaptation to extra-uterine life of newborn infants'.

On the evening of May 4, 1960, the Honorary Secretary reported the results of the preliminary analysis of the replies which had been given to the questionnaire on the paediatric staffing structure in the hospital service. This was followed by a brief discussion.

K. R. Llewellin won the Ulster Cup golf competition.

BOOK REVIEWS

Growing Up in Newcastle upon Tyne: a continuing study of health and illness in young children within their families. By F. J. W. MILLER, S. D. M. COURT, W. S. WALTON and E. G. KNOX. (Pp. 369; illustrated. 25s.) Published for the Nuffield Foundation by the Oxford University Press. 1960.

The Newcastle study was initiated in 1947 by Sir James Spence and his co-workers of the Nuffield Department of Child Health at King's College and the City Health Department with the object of providing a record of the incidence and type of illness occurring in childhood evaluated against a fully studied family and environmental background. It is offered as 'a contribution towards understanding the needs of the family in sickness and in health' as a means of preventing childhood disturbances and illnesses with their associated morbidity and mortality. The study emphasizes throughout the child as an integral part of his family and environment.

The first volume, 'A Thousand Families in Newcastle upon Tyne',* deals with the first year of life of the children in the sample. The new volume is a continuation of this work and presents the progress of 847 of the children from the same thousand family sample during the first five years of life between 1947 and 1952. The book describes the varying social and economic fortunes of the family seen against a background of life in the city and gives a general picture of the patterns of illnesses and deaths during the five years. These are subsequently described in detail and related to various aspects of the child's environment which have been fully considered in terms of housing, family and medical care. The importance of this approach can be seen in the conclusion that 'in infancy, at least, social factors largely determine whether a given infection will develop as a cold, bronchitis or pneumonia'. The significance of the family in the epidemiology of childhood illness is beautifully demonstrated in the family studies of entrenched staphylococcal and streptococcal infections. The analyses of recorded facts are well laid out in the Appendices and a short glossary of medical and local terms is provided. There are some excellent photographs which add to the clear descriptive pictures.

The value of the book lies not only in its clear presentation of the natural history of childhood disease fully evaluated against its environmental and epidemiological background, but in its record of contemporary social life. The care and consideration with which the families have been treated in order to obtain these facts are evident throughout the book and are stressed by the attitude 'We hope that during these years we have been sufficiently sensitive to the privileges we have been so generously given' and also by the degree of cooperation from the families with only seven withdrawals from the survey during the five years. The high incidence of disturbance in the human environment, with 53% of the children having at least one adverse factor in deprivation, deficiency and dependence, and 8·3% of children whose families are deeply involved in all three factors, stresses the real need for family guidance, especially in the sphere of personal relationships. Education of parents with regard to the recognition of illness and the avoidance of contact with cases requires greater attention than has been previously given in order to reduce further illness and morbidity in children. The important role of family doctor emerges in its true light and the need for improved medical education in order to enable him to fulfil this role adequately is made apparent.

It is hoped that as the study advances greater attention might be paid to the physical growth of these children; a few simple measurements accurately taken by health visitors at regular and more frequent intervals would provide a unique opportunity for longitudinal growth study in so large and representative a sample of children whose background and development is intimately known.

This book is strongly recommended to all those concerned with family health, in particular, medical students, family doctors, health visitors and sociologists and to any who seek an outstanding study to provide a model for any similar work.

* Published for the Nuffield Foundation andthe Nuffield Provincial Hospitals Trust, 1954, 10s. 6d.

Brucellosis in England. By HUGH R. E. WALLIS. (Pp. 140; 9 figs; Index. 25s.) London: A. S. O'Connor & Co. Ltd.

Dr. Harold J. Harris states in the preface to this book, 'The case histories given so vividly but with such admirable conservation of verbiage (which indeed pertains throughout the book) serve to call attention to the manifold symptomatology of brucellosis . . .'; unfortunately the greatest fault of this book is its failure to present concise and exact data and observations. Dr. Wallis quotes extensively from the classic paper of Barrett and Rickards but the evidence he presents is not as convincing as was theirs. One of the most interesting sections is the brief historical review.

There are several errors which point to poor editing, which is surprising in a monograph which is obviously a labour of love. It is irritating to find 'see Table 1 on pages 30-31' when Table 1 is on pages 88-89; or to read 'the urine may show a few to many leukocytes'; or that a very good positive skin reaction 'remained for a week and the centre became almost neurotic'. Percentages are often given to the second decimal place but as the thesis is mainly developed on the data from 35 cases, this is hardly justified; it would appear that Dr. Wallis might have been bewitched by his own figures as when he

refers to the examination of 17 specimens of sera, obtained after skin tests had been performed, and he found that '14 (82·35%) showed a significant rise in titre'.

It is stated that blood culture is rarely positive, but it is surprising that there is no mention of a blood culture being performed on Case 4, which was diagnosed early in the disease when the titre of agglutinins was high; the reviewer has always found that such a case has given positive blood cultures.

However, this book emphasizes the importance of excluding a diagnosis of chronic brucellosis in patients who have 'rheumatic' symptoms and it is valuable also because it restates the value of brucellin skin tests when these are combined with serial agglutination reactions; the author also demonstrates the danger inherent in unpasteurized milk.

The Royal Edinburgh Hospital for Sick Children, 1860-1960. By DOUGLAS GUTHRIE with various contributors. (Pp. 75+xii; illustrated. 17s. 6d.) Edinburgh and London: E. and S. Livingstone Ltd. 1960.

The Royal Edinburgh Hospital for Sick Children celebrates its Centenary this year, a fact which will be acclaimed by many outside the intimate circle of those privileged to speak affectionately of the 'Sick Kids'.

The story of this famous hospital is an epic which compels the telling as the first hundredth milestone passes. We must all be grateful to Dr. Douglas Guthrie for his undertaking and congratulate him warmly upon his achievement. He has given us a delightful little book which is assured of world-wide interest.

The author has been assisted by seven other distinguished contributors. This could have been a problem, but any risk of scrappiness or repetition has been skilfully avoided. History unfolds smoothly, crucial episodes and vital personalities are admirably high-lighted, and the result is a most readable record of great historical value. From its birth, a hundred years ago, the Hospital has grown gloriously in the setting of the Edinburgh School of Medicine of which it must always be an essential bulwark. Today state control brings a new challenge, as Professor Ellis indicates in his wise assessment of the future. There are many in the hospital world outside Edinburgh who chafe under the torpor of bureaucracy and pray for a renaissance in high places of the courageous vision which inspired the Voluntary Hospital System. Wherever re-education may be necessary, Dr. Guthrie's book affords a timely stimulus.

Maternal Disorders related to Fetal Stress, Perinatal Death and Congenital Defects. Selected References 1952-58. (Pp. v+33.) Bethesda, Md.: U.S. Dept. of Health, Education and Welfare. Copies available from the Library, National Institutes of Health, Bethesda 14, Maryland, U.S.A.

This list of references is concerned with those maternal disorders which bear on the foetus and the perinatal period and which cause congenital defects. There are some 413 of them but as the articles included are all in the English language, the publication is of rather doubtful value.

Der Liquor Cerebrospinalis in Kindesalter. By H SCHÖNENBERG. (Pp. viii+175; 43 figs. DM. 29. Stuttgart: G. Thieme. 1960.

This is the first comprehensive monograph on the cerebrospinal fluid written by a paediatrician for paediatricians. It is divided into two parts—the first giving the *general* data of physiology and pathology whilst the second contains a full account of the fluid findings in *each disease*. In both parts the presentation of detail and the discussion of the theoretical aspects are well balanced. The main subjects of part one include barriers, testing for permeability, technique of specimen taking, pressure, cells, proteins, electrophoresis, colloid reactions, sugar, sodium chloride, lipins, lactic acid, amino-acids, physico-chemical properties, enzymes, vitamins, immunology, the normal, subnormal and pathological liquor in general and the liquor syndromes (meningitis, encephalitis). The second part is devoted to a description of the fluid changes integrated with the pathology of all known central nervous diseases of childhood including Listeria infection, actinomycosis, leptospirosis, mycoses, toxoplasmosis, foreign body meningitis and viral encephalomyelitis (down to cat-scratch disease).

The author draws from personal experience, and his presentation of the possibilities and limitations of liquor diagnosis is critical. A list of references running to 13 pages concludes the book. It will be welcome to paediatricians and clinical pathologists.

X-ray Diagnosis of the Alimentary Tract in Infants and Children. By EDWARD B. SINGLETON. (Pp. 352. 83s.; 11.00$.) London: Interscience Publishers Ltd. Chicago: Year Book Publishers Inc. 1959.

This is by far the most realistic and comprehensive book on the radiology of the gastro-intestinal tract in children that has yet been published. It is very readable and approaches the subject from the viewpoint of a logical application of radiographic techniques to the problems of children's disease. This is perhaps the chief value of the book. The clinical background, including the developmental, anatomical and physiological factors involved in each problem, is first excellently surveyed. The position of radiology in each case is then given in detail, and the radiological contribution discussed in an unusually able manner against the clinical background. At the end of each section there is a list of references, and the titles and subtitles are clear and numerous.

The illustrations are of the same high quality as the text and excel those found in most textbooks of radiology by concentrating on the problem at issue. They are unusually effective, and there are plenty of them.

This work can be recommended without reservation and will be found of the utmost value to both clinicians and radiologists. It should go far to clear up a lot of the uncertainty that still prevails as to the role radiology plays in the diagnosis of alimentary disease in the young. The author is to be congratulated.

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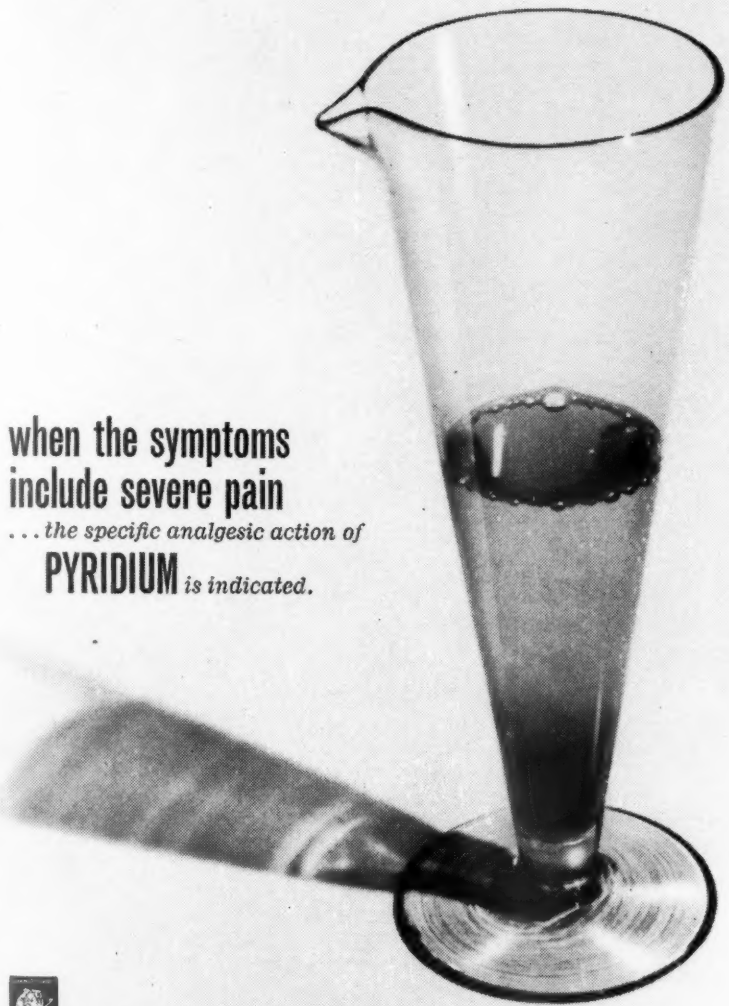

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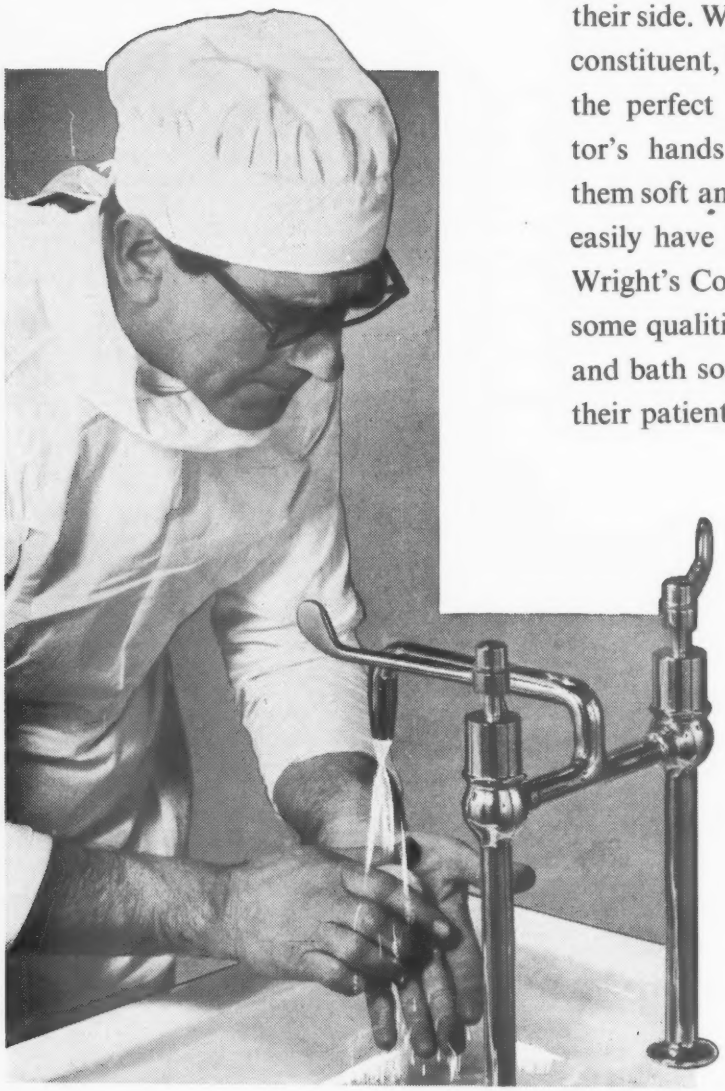

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